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The American Academy of Pediatrics

October 18 to 23, 1952

Palmer House

Chicago

AREAL MEETING

May 22 to 24, 1952

Statler Hotel

Washington, D.C.

Pediatrics

VOLUME 9 MARCH 1952 NUMBER 3

ORIGINAL ARTICLES

DISORDERS OF GLYCOGEN METABOLISM

With Special Reference to Glycogen Storage Disease and Galactosemia

By WILLIAM H. LANGEWISCH, M.D., AND JOHN A. BIGLER, M.D
Chicago

THE terminology and differentiation of the various types of glycogen storage disease and of cases of hepatomegaly with evidence of disturbed carbohydrate metabolism has always been difficult. Mason and Anderson[1] attempted to classify the cases which have been described under the heading of glycogen disease by dividing them into five distinct groups. The first group consisted of glycogen storage disease of the liver (von Gierke's disease). The second group included glycogen storage disease of the heart and muscles. Cases of galactosemia (galactose diabetes) constituted the third group, whereas the fourth and fifth groups consisted of a variety of diseases with associated increased glycogen deposits in the liver.

Recent investigations, however, have thrown some doubt upon the advisability of including galactosemia as a type of glycogen storage disease. Bell, Blair, Lindsay and Watson[2-3] have shown quite conclusively that the hepatic enlargement and dysfunction which is present in these cases is due to fatty infiltration of the parenchymal cells. It was formerly assumed that the hepatomegaly was due to excessive storage of glycogen or galactose. Galactosemia still deserves consideration along with the hepatic and cardiac types of glycogen storage disease because all three conditions represent a defect in the enzymatic conversion of a monosaccharide to glycogen and/or its subsequent conversion back to glucose. Moreover, in all these diseases there is an accumulation of an abnormally large amount of stored material (i.e., fat or glcogen) in specific body cells resulting in organ enlargement and dysfunction.

During the past nine years, five examples of disordered glycogen metabolism have been investigated at The Children's Memorial Hospital. These cases are presented because of their rarity and interest. They fall within the first three groups of Mason and Anderson's[1] classification.

From The Children's Memorial Hospital, Chicago.
(Received for publication July 31, 1951.)

Glycogen Storage Disease of the Liver (Von Gierke's Disease)

Over 50 cases of the hepatic form of glycogen storage disease have been reported since von Gierke's original description in 1929. Mason and Anderson[1] found only 34 cases in which they considered the diagnosis to be without question. Other authors, such as van Creveld,[4] have reported a much larger number, but it is very doubtful whether all these are true examples of this syndrome. Di Sant' Agnese, Anderson and Mason[5] have recently re-emphasized the fact that the hepatic and cardiac types of glycogen storage disease are separate entities which do not coexist. The two diseases are similar in that they both exhibit a familial tendency but it is only in the hepatic type that laboratory and clinical evidence of disordered glycogen metabolism may be obtained. Diagnosis of the hepatic type depends upon the following findings: marked hepatomegaly, rapid development of hypoglycemia and ketonuria when food is withheld, a subnormal or absent response of the blood sugar to subcutaneously injected adrenalin, and the demonstration of abnormally large amounts of glycogen within the liver by chemical or histochemical methods. Bridge and Holt[6] believe that the demonstration of abnormal stability of the liver glycogen in vitro or after death is also necessary for the diagnosis, but this has been regarded as merely confirmatory by others.

Additional laboratory evidence of the presence of glycogen storage disease of the liver may be obtained by investigation of the patient's carbohydrate and fat metabolism. The blood lactate is frequently elevated when the subject is in a resting condition. The blood glycogen is usually increased. An insulin tolerance test will generally reveal unresponsiveness to hypoglycemia and a dextrose tolerance curve produces a high prolonged rise. In some cases, however (see below), administration of oral dextrose results in a high biphasic curve as noted by van Creveld.[7] The serum lipids and cholesterol are frequently increased during the early stages of the disease. The following two cases are representative of this condition.

Case Report

J. J., a 19 mo. old white female, referred by Dr. Knowlton Barber, was admitted to The Children's Memorial Hospital because of an enlarged abdomen which had been present since birth. The child had been generally well except for the presence of 4 major convulsions during the previous 3 mo., all occurring in the early afternoon while the child was sleeping. In addition, the patient's development had been somewhat retarded, and the child still did not pull herself up to a sitting position or attempt to stand at the time of admission to the hospital.

The birth history was normal, and the child had had no difficulty in the neonatal period. Weight gain had been slow however, the admission weight being only 9.1 kg. in spite of an apparently adequate food intake. The parents and one sibling were living and well, and there was no evidence of hereditary disease.

Physical examination revealed a small irritable child. The findings were not remarkable except for the abdomen which was obviously protuberant. A large mass was palpable in the right side which was continuous with the liver and fairly smooth. The edge of the mass could be felt below the iliac crest in the right lower quadrant, extending superiorly and to the left.

RGs revealed the mass to be anterior, pushing the barium-filled right colon medially. An intravenous pyelogram was normal.

Laboratory examinations revealed the patient to have a normal blood count except for a moderate anemia of 3.8 million RBC/cmm. The urine was consistently negative, with the exception of acetone. The prothrombin time was normal. The icterus index was 18, total protein 7.1 gm/100 cc., A-G ration 4.55/2.55, cholesterol 385 mg./100 cc. and the cephalin flocculation was negative. The sedimentation rate was 27 mm./hr. (Cutler) and hematocrit 33%.

An oral glucose tolerance test (1.75 gm. glucose/kg. body weight) revealed a fasting hypoglycemia and biphasic prolonged curve (chart 2). (Fasting—29.4 mg./100 cc., ½ hr.—131.6 mg./100 cc.,

1 hr.—98.5 mg./100 cc., 2 hr.—126.6 mg./100 cc., 3 hr.—112 mg./100 cc.*) There was no response to subcutaneously injected adrenalin—0.25 cc. 1:1000 aqueous solution. (Fasting—36 mg./100 cc., ½ hr. after injection—27 mg./100 cc.)

In view of these findings a biopsy was obtained with the preoperative diagnosis of glycogen storage disease of the liver. The liver was large, firm and yellowish mottled. The remainder of the abdominal cavity appeared normal. Microscopic examination of the biopsy specimen stained with hemotoxylineosin and Best's carmine revealed huge, coarsely vacuolated hepatic cells, with distinct nuclei and cell membranes (Fig. 1). The findings were interpreted as being compatible with glycogen storage disease of the liver. Glycogen granules were not demonstrated, however, because the specimen had been placed in a formalin solution before being stained.

The child's postoperative course was uneventful and she was discharged 20 days after admission. Further studies at the University of Minnesota Medical School by Dr. Irvine McQuarrie revealed

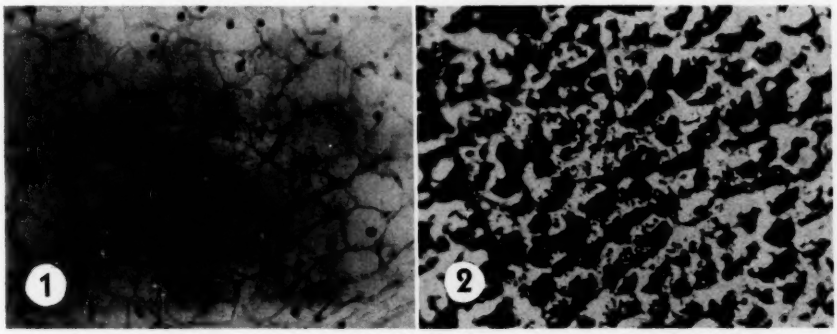


FIG. 1. Photomicrograph (high power) of liver biopsy in Case J. J. showing large, coarsely vacuolated hepatic cells (hemotoxylin-eosin stain).

FIG. 2. Photomicrograph (high power) of liver biopsy in Case T. G. showing glycogen droplets within liver cells. Dark areas are masses of deeply staining glycogen material (periodic acid stain).

similar laboratory evidence of glycogen storage disease. A poor glycogenolytic response to subcutaneously injected adrenalin was obtained in addition to a biphasic, diabetic-like oral glucose tolerance test. Treatment with adrenocorticotrophic hormone abolished the fasting hypoglycemia during the period of therapy on 2 occasions. On both occasions, withdrawal of ACTH caused return of the hypoglycemia. The patient's total eosinophil count remained low both during the preliminary period and during the period of ACTH administration. On withdrawal of the hormone, however, the eosinophil count rose to 400/cmm. Acetonuria disappeared during the 11 day period of ACTH therapy. The patient's general clinical reaction appeared to be improved greatly during this period. Her appetite improved strikingly and she was much more cooperative (chart 1).

CASE REPORT 2

T. G., a 4½ mo. old white male infant. An enlarged liver had been found upon routine physical examination the day prior to admission. The child had never been ill. Its development appeared normal. The mother's pregnancy had been normal and the labor, delivery and neonatal period were without notable incident. The infant had taken its formula well and had gained weight readily. The family was well and without history of hereditary disease.

Physical examination revealed a well-developed, 6.9 kg. infant in no apparent distress. The pertinent findings were confined to the abdomen where the liver was found to be enlarged and firm. Its edge was smooth and at the level of the umbilicus. The kidneys and spleen were not palpable. Glycogen storage disease of the liver was considered as the most likely diagnosis.

The child's blood count revealed Hgb. of 10.5 gm./100 cc. and RBC 4.0 million/cmm. The total WBC count and differential count were normal. The urine was free from formed elements, sugar or albumin. The serology was negative. Blood chemistries revealed NPN 29 mg./100 cc., cholesterol

* Folin-Wu Method

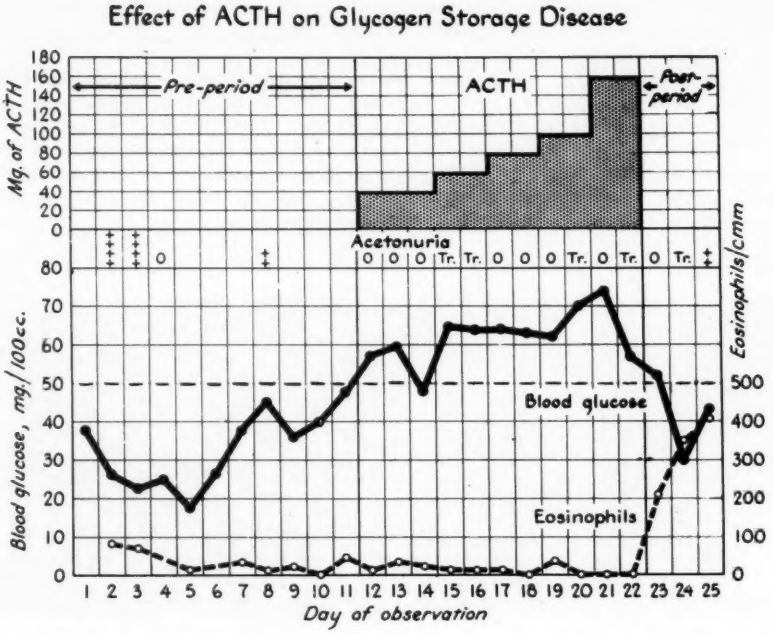


CHART 1. Graph showing disappearance of hypoglycemia and acetonuria during period of ACTH therapy in Case J. J. Note prompt rise in eosinophils after therapy was discontinued. (Courtesy of Dr. Irvine McQuarrie.)

of 225 mg./100 cc., cholesterol esters 123 mg./100 cc., or 55% of total, total protein 4.8 gm./100 cc., albumin 2.6 gm./100 cc., globulin 2.2 gm./100 cc., glycogen 15 mg./100 cc. and a negative cephalin flocculation. An oral glucose tolerance test (1.75 gm. glucose/kg. body weight) revealed a fasting hypoglycemia and a high prolonged curve (fasting—41 mg./100 cc., ½ hr.—91 mg./100 cc., 1 hr.—161 mg./100 cc., 3 hr.—124 mg./100 cc., 5 hr.—77 mg./100 cc., chart 2). No response to subcutaneously injected adrenalin (0.3 cc. 1:1000 aqueous solution) was noted. (Fasting—49 mg./100 cc., 15 min.—49 mg./100 cc., 30 min.—43 mg./100 cc., 60 min.—48 mg./100 cc., 120 min.—54 mg./100 cc.) Urinary acetone was noted to be 4+ prior to and following the adrenalin test.

An intramuscular pyelogram and "scout" film of the abdomen revealed the mass to be enlarged liver. Both kidneys visualized well and appeared normal in size, shape and position.

These findings were regarded as being compatible with glycogen storage disease of the liver.

A confirmatory biopsy revealed the liver to be light brown in color and fairly soft to the touch. The microscopic sections demonstrated normal lobular architecture. The cytoplasm in the routine hemotoxylin and eosin stain appeared to be scanty and reticulated in appearance with almost complete absence of staining. With periodic acid glycogen stain, it was obvious that the nonstaining areas were filled with small droplets of glycogen. No excessive fibrosis or cellular infiltration was present (Fig. 2).

Diagnosis: Biopsy of liver showing glycogen storage disease.

COMMENT

Although glycogen was not demonstrated in one of the biopsies reported here (J. J.) because of previous fixation of the specimen in formalin solution, the authors believe the case is sufficiently typical in other respects to be included in this series. The appearance of even the hemotoxylin-eosin stained specimen is characteristic. The physical findings and

laboratory studies are likewise typical. This case is of additional interest because of the studies performed by Dr. Irvine McQuarrie. His work clearly indicates that the acetonuria and hypoglycemia in this disease may be abolished by sufficient doses of ACTH when the hormone is administered every six hours. Larger doses were required than in other hypoglycemic states. This suggests a partial refractoriness to the hormone.* The clinical manifestations of the hepatic type of glycogen storage disease are well demonstrated in the two cases presented here. Despite the fact that the condition probably begins in utero, the presence of an enlarged liver may not be noted until several months after birth. Symptoms due to hypoglycemia are frequently present and may be the factor which prompts investigation of the condition. The child's nutrition is usually fairly good, and

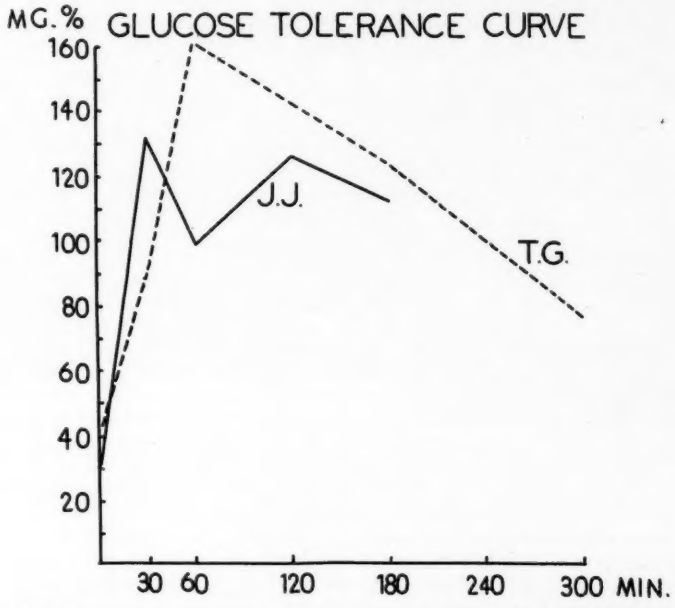


CHART 2. Oral glucose tolerance curves in Cases J. J. and T. G., illustrating 2 different types of glucose tolerance curves which may be found in glycogen storage disease of liver.

even obesity may be present. Some degree of physical retardation is common. Occasionally, a child with this disease may exhibit a marked preference for foods high in carbohydrates.

The prognosis of this variety of glycogen disease is much better than that of the cardiac type. The patient may live for several years and then succumb to an intercurrent infection or acidosis. There are a number of reports in the literature of spontaneous cure at or about puberty. Dietary therapy may result in some improvement of symptoms. Lowrey and Wilson[8] have recently reported a case of glycogen storage disease of the liver with dramatic relief of hypoglycemic symptoms by the use of a high protein, low carbohydrate diet.

In contrast to the widespread deposition of glycogen which is found in cases with the cardiac type of glycogen disease, patients with the hepatic type reveal excess glycogen only

* Reported by Dr. Irvine McQuarrie at the Second Clinical ACTH Conference in Chicago.

in the liver and kidneys. The reason for the increased amount of glycogen in the kidney is obscure. Van Creveld[4] has suggested that it may be due to an attempt upon the part of the kidney to excrete the increased amount of glycogen which is found in the blood.

Glycogen Storage Disease of the Heart

This entity has recently been reviewed by di Sant' Agnese, Anderson and Mason.[5] These workers have found only 12 proved cases in a careful search of the literature, not counting the two cases which they reported in siblings. An additional case has been reported by Clement and Godman.[9]

A large number of conditions may cause cardiac enlargement and increased deposition of glycogen within the myocardial fibers. In order to separate true cases of glycogen storage disease of the heart from other pathologic entities di Sant' Agnese et al.[5] established the following requirements to be fulfilled:

1. Marked enlargement of the heart.
2. Death within the first year of life.
3. Typical "lacework" appearance of histologic sections of myocardium resulting from massive deposition of stored material in all cardiac fibers.
4. Chemical or histochemical demonstration of glycogen as the material causing infiltration of stored material in all cardiac fibers.

The above requirements are fulfilled by the following two cases:

Case Report 3

J. O., an 8 mo. old white male infant, was admitted to The Children's Memorial Hospital with a history of difficult breathing for 4 days, pallor and general "poor health" for 2 mo., and frequent vomiting for 1 wk. The child had been born approximately 3 wk. prematurely and weighed 2.3 kg. at birth. Delivery and the neonatal period were uneventful except for several blood transfusions during the first week of life. Frequent formula changes had been tried because of slow weight gain and recurrent vomiting. The family, including a 3 yr. old sibling, appeared to be well.

Physical examination at the time of admission revealed a pale 6.4 kg. infant who appeared moribund. Breathing was difficult and grunting in nature. The heart was greatly enlarged, but no murmurs were present. The tones were rapid and regular. Bronchial breathing was present throughout both lungs, with decreased resonance on the life side of the chest. The liver was enlarged, the edge being felt about 4 cm. below the right costal margin. The spleen was not palpable.

RG examination of the chest revealed a large globular heart. A diagnosis of von Gierke's disease was suggested because of the cardiohepatomegaly. Laboratory examinations revealed Hgb. 5.8 gm./100 cc., RBC count 3.5 million/cmm. and WBC count of 24.7 thousand/cmm. with a normal differential. Serology was negative. NPN was 81 mg./100 cc., cholesterol 118 mg./100 cc., blood sugar 25 mg./100 cc., carbon dioxide combining power 18.4 vol.%. Blood culture was negative. In spite of intravenous fluids, oxygen and stimulants, the child died 2 hr. and 20 min. after admission to the hospital.

An autopsy, which was confined to the trunk, revealed the heart and pericardium to occupy about ⅔ of the transverse diameter of the chest. Approximately 50 cc. of blood-tinged, sterile fluid was found in the pericardial cavity. The heart was globular in shape with a large, firm, contracted left ventricle and a tremendously dilated right auricle. Its weight was 120 gm. (normal 37 gm.) with a thick (7 to 10 mm.) left ventricle and thin (2 mm.) right ventricle. The myocardium was pale pink in color. The valves appeared normal, the tricuspid measuring 5.5 cm., in circumference, the pulmonary 3.4 cm., the mitral 2.8 cm., the aortic 2.4 cm. The foramen ovale and ductus arteriosus were closed. No septal defects were present and the coronary orifices appeared normal. The great vessels made a normal exit.

The liver appeared to be grossly normal in size, weight, color and consistency. The kidneys were of normal size but of a pale yellow color. The other organs were not remarkable.

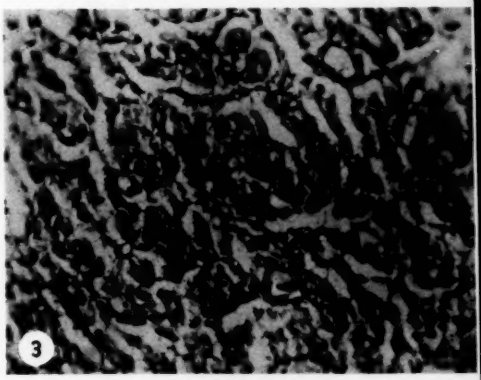
Microscopic examination of the myocardium revealed the myocardial fibers to be composed of a vacuolated cytoplasm with distinct nuclei. The many clear spaces were delineated by a fine lacy net-

work which extended throughout the cell. With periodic acid stain, it was evident that the clear areas were filled with glycogen granules (Fig. 3). Glycogen could also be demonstrated in the interstitial spaces.

Congestion, central necrosis and fine vacuolization was demonstrable in the hepatic cells. No glycogen excess was seen in the liver or in the skeletal muscle (diaphragm and psoas), even with the use of special stains.

Sections of the kidney revealed the cells of the collecting tubules to be swollen and granular. With Best's carmine stain, glycogen could easily be demonstrated occupying the clear areas of a vacuolated cytoplasm.

Autopsy Diagnosis: 1. Glycogen storage disease of the heart; 2. Glycogen deposits in the kidney tubules.



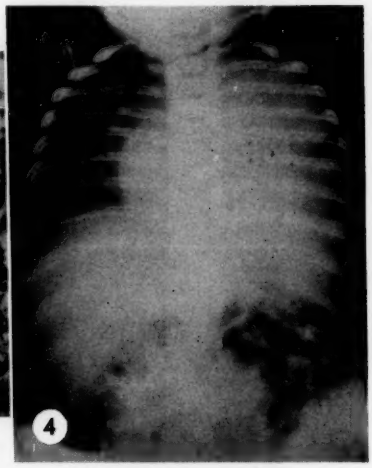


FIG. 3. Photomicrograph (high power) of heart in Case J. O. revealing droplets of deeply staining glycogen within myocardial fibers (periodic acid stain).

FIG. 4. Chest RG in Case S. H. revealing massive cardiac enlargement present in glycogen storage disease of heart.

CASE REPORT 4

S. H., a 4½ mo. old white female infant, entered The Children's Memorial Hospital with the presenting complaint of cough and shortness of breath of 3 wk.' duration. This difficulty appeared to be associated with an upper respiratory infection; but when the child failed to improve, RG was taken which revealed an opacity filling the entire left side of the chest. A thorocentesis was attempted by an outside physician, but no fluid was obtained. The child was then referred to The Children's Memorial Hospital. The past history did not appear remarkable except for a poor appetite and slow weight gain. The patient's birth history appeared normal, and her parents were both living and well. No immunizations had been received. Development seemed to be proceeding at the expected rate. Physical examination at the time of admission revealed a slender, irritable child weighing 5.6 kg. Her pulse was 88/min. and respirations 50/min. The pertinent physical findings were confined to the chest and abdomen. The left chest was more full anteriorly than the right. Percussion revealed the entire left chest to be dull, together with markedly diminished breath sounds to auscultation. The heart appeared to be enormously enlarged, with a large part of the left chest heaving with each heart beat. The heart sounds were somewhat faint, but a definite, moderately loud systolic murmur could be heard over the precordium. This murmur was not well localized, and could also be heard posteriorly when the breathing was quiet. The right chest appeared to be normal. The femoral pulses were easily palpable. The liver was felt about 3 cm. below the right costal margin, but did not seem to be particularly firm. The spleen was not palpable.

Laboratory examination revealed RBC count 3.9 million/cmm. with Hgb. 9.2/100 cc. The WBC

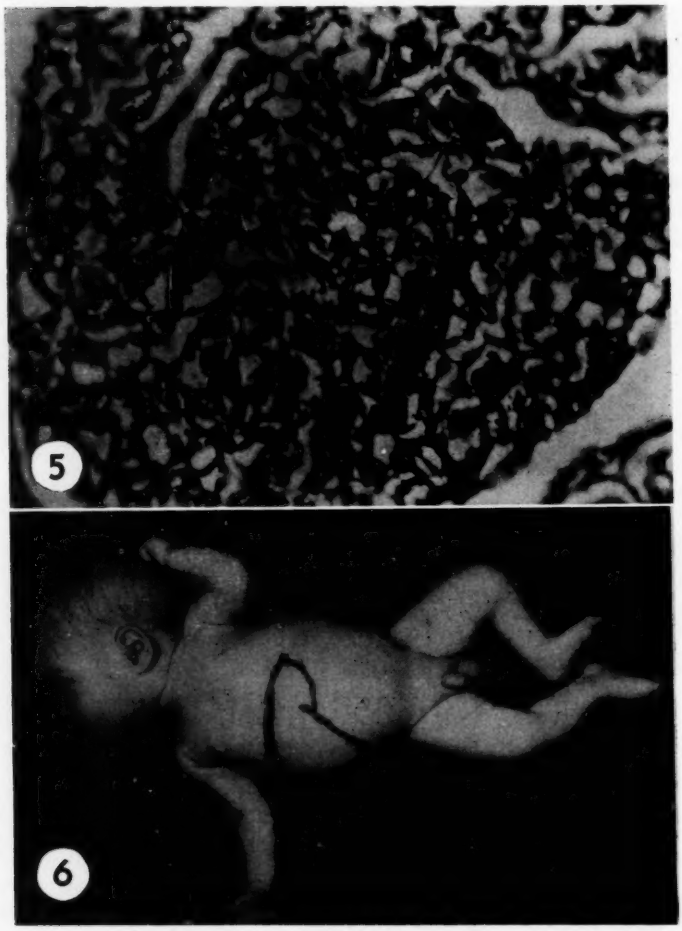


FIG. 5. Photomicrograph (high power) of heart in Case S. H. revealing deeply staining glycogen droplets within myocardial fibers (periodic acid stain).
FIG. 6. Case M. M. Massive hepatomegaly and protuberant abdomen.

count was 13.3 thousand/cmm. with a normal differential count. The urine was reported as normal, but was not tested for acetone.

RGs and fluoroscopy of the heart revealed the left chest to be completely opaque with a slight shift of the mediastinum to the right. The cardiac contour could not be distinguished (Fig. 4). ECG revealed combined heart strain and was interpreted as being definitely abnormal and compatible with congenital heart disease.

The complete report is as follows: "P-R interval 0.11. Rate 100 min. Sinus rhythm. P-wave is upright and notched in lead 1, upright and peaked in lead 2, diphasic in lead 3. QRS complex is mainly upright and 'W shaped' in the limb leads with a prominent Q-wave in leads 2 and 3. S-T segment is abnormally depressed in the limb leads. T-wave is inverted in the limb leads. The P-wave is diphasic in the chest leads. The QRS complex is widely diphasic in leads CF_2 and CF_4, triphasic with

a tiny Q-wave and S-wave in lead CF_5. S-T segment is abnormally elevated in lead CF_2. T-wave is upright in lead CF_2, inverted or diphasic in CF_4, diphasic in CF_5."*

Bronchoscopic examination revealed extreme compression of the left main bronchus which was regarded as being extrabronchial in origin.

Because of the possibility of an extracardiac tumor mass in the chest, the child was scheduled for an exploratory operation. She died during the preoperative preparations.

Postmortem examination revealed a massively enlarged heart which filled almost the entire left chest. Its weight was 180 gm. (normal 29 gm). The apex contacted the parietal pleura on the left side. There was only a small amount of pericardial fluid and the great vessels were in the normal position. The foramen ovale was anatomically closed and the interventricular septum was intact. The ductus arteriosus was closed. The coronary arteries were normal in their origin and course. The myocardium seemed slightly more pale than normal. The right ventricle appeared to be moderately enlarged, and the left ventricle was enormously dilated and hypertrophied (20 mm. thick). The valves were normal structurally, the tricuspid measuring 22 mm. in circumference, the pulmonary 34 mm., the mitral 41 mm. and the aortic 26 mm.

Microscopic examination revealed the myocardial fibers to be unusual in that they were somewhat enlarged with central vacuolization. Many of the nuclei had been displaced peripherally. Glycogen stains (periodic acid) revealed the central vacuolated material to contain large amounts of glycogen (Fig. 5).

The liver was found to be moderately enlarged and pale in appearance. The cytoplasm of the hepatic cells had been replaced by large vacuoles, leaving only the peripheral cell membrane distinguishable. Within the cell membranes there was a fine feathery-like material which was revealed to contain many glycogen granules. No fibrous or cellular reaction was present.

The kidneys were not remarkable in gross appearance, but microscopic examination revealed the medullary portion to contain large amounts of glycogen within the tubular epithelium. These cells were large and swollen, and their cytoplasm was completely replaced by large vacuoles. The skeletal muscle did not reveal increased amounts of glycogen.

Diagnosis: Glycogen storage disease involving the heart, liver and kidneys.

Comment

These two cases do not differ from those previously reported and recently reviewed by di Sant' Agnese, Anderson and Mason.[5] In both instances the heart was enormously enlarged and filled a large part of the chest. It is of interest to note that the cardiac enlargement in one case (S. H.) was so massive that pleural fluid was suspected by the referring physician and aspiration was attempted. An extracardiac mass was still considered a possibility after the diagnostic work-up had been completed.

The pathologic observations are typical of glycogen storage disease of the heart. As noted in previous reports, deposition of glycogen is not confined to the myocardium. Smooth and skeletal muscle, the cells of the reticuloendothelial system, liver, kidneys, pancreas, adrenal, and the mucous cells of the gastrointestinal tract may all reveal excess glycogen deposition. The presence of glycogen deposits in the central nervous system has recently been re-emphasized by Clement and Godman.[9] In the cases reported here, excess glycogen was noted in the liver (one case) and kidneys (both cases).

The physical examination of patients with this disease frequently reveals marked malnutrition, accompanied by cyanosis and dyspnea in the more terminal stages. The child may be a "poor feeder" and fail to gain weight. Macroglossia and generalized muscular hypotonia may lead to a mistaken diagnosis of cretinism, mongolism or amyotonia congenita. The hypoglycemia and ketosis which are so characteristic of the hepatic form of glycogen disease are invariably absent. Other laboratory examinations are likewise normal.

* Electrocardiographic interpretation courtesy of Dr. Jakub G. Schlichter and Dr. C. R. Leininger.

The prognosis is invariably fatal. Death from heart failure usually occurs within the first eight months of life.

The ECG in this disease is of considerable interest. Di Sant' Agnese, Anderson and Mason[5] state that only three of the reported cases include electrocardiographic studies. Clement and Godman[9] have added an additional ECG, and also include the ECG of Antopol, Boas, Levison and Tuchman[10] in their discussion. This case, however, is in a 15 year old boy and does not meet the requirements for the diagnosis of glycogen storage disease of the heart as outlined by di Sant' Agnese, Anderson and Mason.[5]

The specific ECG findings in this condition usually include a low S-T segment take-off and inversion of the T-waves in several of the limb leads. Left axis deviation may be present, or there may be no axis deviation at all. The absence of right axis deviation in itself is abnormal at this age and equivalent to left axis deviation in older children and adults.

In the present authors' case there was evidence of combined heart strain, accompanied by inversion of the T-waves and an abnormally depressed S-T segment in all limb leads.

It is impossible to make the diagnosis of glycogen storage disease of the heart on the basis of electrocardiographic findings alone. Other conditions, such as anomalous origin of the coronary artery, which are characterized by myocardial hypertrophy, may result in similar ECG findings.

Galactosemia (Galactose Diabetes)

The literature on galactosemia has been recently reviewed by Bell, Blair, Lindsay and Watson.[2] They report a clinicopathologic study of two siblings with this disease. Prior to their study only 15 cases of this interesting syndrome had been described and the diagnosis appears to be in doubt in at least three instances. DuShane and Hartman[11] have recently reported a case followed for 24 months with good development. A marked familial tendency was noted in 3 of the 4 cases reported by Donnell and Lann,[12] and in 2 of the 5 cases reported by Townsend, Mason and Strong.[13]

The following case is illustrative of this condition.

Case Report 5

M. M., a white male infant, was delivered by cesarean section, which was performed during the eighth month of gestation because of toxemia. This was the mother's first pregnancy. There was no history of familial disease. The child weighed 3.5 kg. at birth and its immediate postnatal condition appeared to be good. Feedings of evaporated cow's milk were started on the second day of life but the child seemed to be listless and took feedings poorly. On the sixth day of life, the child was started upon breast feedings with frequent gavage feedings of breast milk. Despite those measures continuous weight loss occurred, and subcutaneous fluids were administered. On the ninth day of life, moderate jaundice was noted, but this seemed to disappear within the next 3 days. Feedings of condensed milk were begun on the tenth day of life, when the child's weight had decreased to 3.0 kg. At this time however, a urinalysis revealed both sugar and albumin in the urine. Repeated examination of the urine continued to be positive for sugar and albumin, although a slow weight gain occurred. The child continued to be listless however, and did not respond to stimuli in a normal fashion. At 4 wk. of age, a mass was discovered in the right upper quadrant of the abdomen, which was interpreted as liver. A transfer was arranged to The Children's Memorial Hospital.

Physical examination on the day of admission revealed a poorly nourished, seemingly alert, 7 wk. old infant weighing 3.5 kg. The pertinent physical findings were confined to the abdomen, where the superficial veins seemed to be more prominent than usual. The liver was palpable approximately 5 cm. below the right costal margin with a firm edge running obliquely across the epigastrium (Fig. 6). The edge of the spleen was just palpable below the left costal margin. A presumptive diagnosis of galactosemia was made.

Course

The presence of albuminuria and melituria was confirmed by repeated urinalysis. The presence of bilateral lamellar cataracts was noted on the 13th day. The cataracts were exactly the same in each eye and involved a large portion of the center of the lens. The patient was later examined by Dr. Richard Gamble, who noted that the infantile nucleus was involved, indicating that the process must have occurred close to the time of birth.

Laboratory tests on the seventh day indicated that the urinary sugar was nonfermentable and definitely galactose (see laboratory findings). Normal plasma proteins, cholesterol and cholesterol esters were present. The glucose tolerance curve was high and prolonged due to high blood galactose levels.

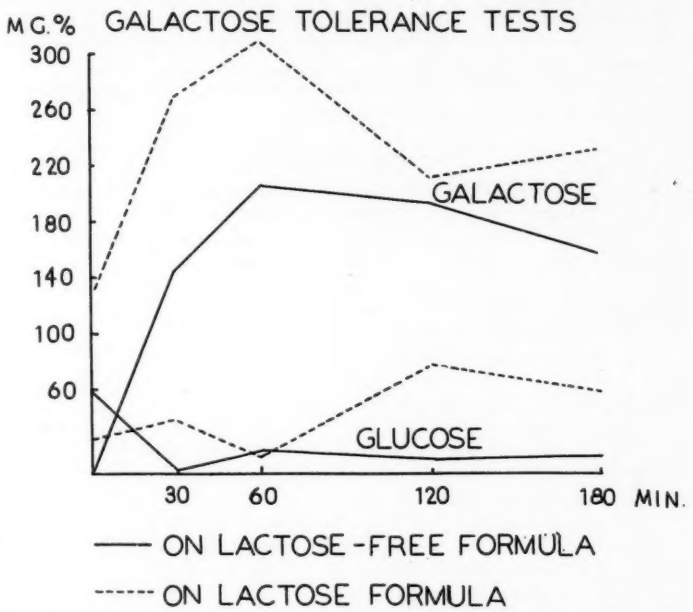


CHART 3. Oral galactose tolerance curves in Case M. M. on lactose-containing and lactose-free formulas. Note depression of blood glucose levels associated with high blood galactose levels.

A prolonged prothrombin time and positive cephalin flocculation revealed the presence of liver damage. A moderate anemia was demonstrated. RGs of the chest and long bones were not remarkable. An intramuscular pyelogram was interpreted as normal.

Because of the patient's poor general condition and absence of weight gain, the child was placed on a mull-soy®* formula on the 13th hospital day. At this time, the child weighed the same as on admission, 3.5 kg.

A prompt weight gain occurred. Within 3 days reducing substance disappeared from the urine, while albumin disappeared by the fifth day. On the 17th day a rather marked, generalized, pitting edema appeared, accompanied by a decrease in the plasma proteins to 3.3 gm./100 cc. This subsided in 1 wk. with the aid of plasma and blood transfusions. The following day a nutramigen®† formula was begun. After a series of diagnostic tests (see laboratory records), the patient was changed back to an evaporated milk formula on the 27th day. At this time, the child weighed 3.9 kg. The cephalin flocculation test, prothrombin time and plasma proteins had reverted to normal. The day after the lactose-containing

* Mull-soy® is a lactose-free soy bean milk.

† Nutramigen® is a lactose-free milk containing hydrolyzed casein combined with balanced amounts of carbohydrate, fat and minerals.

formula was started, galactose appeared in the urine. Albumin appeared in the urine after 5 days on the cow's milk formula. A repeat galactose tolerance test revealed continued intolerance to ingested galactose (chart 3). An adrenalin test revealed a normal glycogenolytic response. No evidence of abnormal bromsulphalein retention was present and the van den Bergh test revealed a negative direct reaction. The cephalin flocculation test and prothrombin time again became abnormal.

The child was again placed on a lactose-free formula (nutramigen®). His weight at this time was 3.6 kg. A prompt weight gain occurred with an increase of 0.2 kg. during the next week.

As observed previously, the galactose disappeared from the urine in one day, while the albumin took several more days to disappear. The cephalin flocculation became negative as before and the prothrombin time became normal. After 1½ mo., the child was discharged from the hospital on a nutramigen® formula, with bananas and cereal as additional foods. At this time, the liver was still enlarged and firm, palpable 5 cm. below the right costal margin. The cataracts were still present, and possibly a little more extensive than when first noted.

Follow-up visits to the outpatient department revealed continuous weight gain and excellent general condition, with some decrease in the size of the cataracts.

Laboratory Examinations

Feeding Period No. 1 (lactose-containing formula . . . evaporated milk) 1–25–51 to 2–7–51

1. Blood

	Hgb. (gm.)	RBC (million)	Platelet	WBC	Polym.	Lymph.	Mono.
1–26–51	8.5	3.74	327,000	10,350	52	47	1

2. Urine
   a. Albumin (24 hr. specs.)
      1–31–51 53.4 mg. in 267 cc.
      2– 2–51 29.8 mg. in 298 cc.
      2– 6–51 46.2 mg. in 185 cc.
   b. Reducing substance (24 hr. specs.)
      1–31–51 Nonfermentable 6.02 gm.
      Fermentable 1.00 gm.
      (Note: urine was not boiled before fermentation)
      2– 2–51 Nonfermentable 4.55 gm.
      Fermentable 0.15 gm.
      (Note: urine was boiled before fermentation)
      2– 6–51 Nonfermentable 5.10 gm.
      Fermentable 0.0 gm.
   c. Qualitative Tests on Urinary Sugar
      Seliwanoff tests (for levulose)—negative
      Tauber's test (for pentose)—negative
      Mucic acid test (for lactose and galactose)—positive
      Rubner test (rules out lactose)—positive
3. Blood Chemistry
      1–26–51 NPN 31 mg./100 cc.
      Cholesterol 132 mg./100 cc.
      Cholesterol esters 85 mg./100 cc. or 64.3% of total
      Reducing substances 145 mg./100 cc.
      Calcium 11.5 mg./100 cc.
      Phosphorous 3.7 mg./100 cc.
      Total protein 5.0 gm./100 cc.
      Albumin 3.0 gm./100 cc., globulin 2.0 gm./100 cc.
      Cephalin flocculation—1+
      2– 2–51 Prothrombin time—over 3 min. (control 21 sec.)
4. Tolerance Tests (while on evaporated milk)
      Glucose tolerance test (oral)*
      1.75 gm./kg. body wt.

* Folin micromethod.

1–29–51

Fasting	176 mg./100 cc.
30 min.	273
60. min.	350
120 min.	298
180 min.	179

Feeding Period No. 2 (lactose-free formula . . . mull-soy®) 2–7–51 to 2–21–51

1. Blood

	Hgb. (gm.)	RBC (million)
2–15–51	7.4	2.82

2. Urine

2–10–51 Albumin 3+, reducing substance negative
2–12–51 Albumin negative, reducing substance negative

3. Blood Chemistry

2–12–51 Total protein 3.3 gm./100 cc.
Albumin 2.3 gm./100 cc., globulin 1.0 gm./100 cc.
Cephaline flocculation—negative
2–19–51 Total protein 4.5 gm./100 cc.
Albumin 2.7 gm./100 cc., globulin 1.8 gm./100 cc.
2–20–51 Bromosulphalein test—10% retention in 30 min.
(dose—2 mg./kg.)
2–21–51 Prothrombin time—17 sec. (control—17 sec.)
Carbon dioxide combining power 46.6 vol.%
Icterus index 10
Van den Bergh test
—direct negative
—indirect moderate immediate positive

4. Tolerance Tests (mull-soy® formula)

a. Glucose tolerance test (oral)
1.75 gm./kg. body weight

2–16–51

Fasting	86 mg./100 cc.
30 min.	138
60 min.	69
120 min.	64
180 min.	71

b. Adrenalin test
0.3 cc. 1:1000 aqueous adrenalin SubQ

2–21–51

Fasting	96 mg./100 cc.
30 min.	162
60 min.	216
120 min.	89

c. Galactose Tolerance Tests (oral)* (while on mull-soy® formula)
1.75 gm./kg. body weight

2–19–51

	Fermentable (glucose)	Nonfermentable (galactose)
Fasting	59 mg./100 cc.	0 mg./100 cc.
30 min.	2	145
60 min.	17	205
120 min.	10	193
180 min.	12	157

(See chart 3)

* According to the method of Roe and Schwartzman.

Feeding Period No. 3 (lactose-containing formula . . . evaporated milk) 2–21–51 to 2–27–51

1. Blood

	Hgb. (gm.)	RBC (million)	
2–22–51	9.75	4.12	(after transfusion)

2. Urine

2–22–51 Albumin negative, reducing substance 4+
2–26–51 Albumin 4+, reducing substance 4+

3. Blood Chemistry

2–26–51 Total protein 6.12 gm./100 cc.
Albumin 4.7 gm./100 cc., globulin 1.5 gm./100 cc.
Icterus index 5
Van den Bergh test
—direct negative
—indirect faint immediate positive
Cephalin flocculation—1+
2–27–51 Prothrombin time—3+ min. (control 18 sec.)
Bromsulphalein test—10% retention in 30 min.

4. Tolerance Tests

Galactose Tolerance Test (oral)
1.75 gm./kg. body weight

	Evaporated milk formula		Control Test on 8.6 kg. infant Evaporated milk formula	
	Fermentable (glucose)	Nonfermentable (galactose)	Fermentable (glucose)	Nonfermentable (galactose)
Fasting	25 mg./100 cc.	126 mg./100 cc.	80 mg./100 cc.	0 mg./100 cc.
30 min.	39	268	60	28
60 min.	12	310	61	34
120 min.	78	212	64	27
180 min.	60	232	90	21

Feeding Period No. 4 (lactose-free formula . . . nutramigen®) 2–27–51 to 3–7–51

1. Urine

2–28–51 Albumin 3+, reducing substance negative
3– 3–51 Albumin negative, reducing substance negative

2. Blood Chemistry

3– 5–51 Cephalin flocculation—negative
Icterus index 4
3– 6–51 Prothrombin time—17 sec. (control 17 sec.)

Comment

This case reveals many of the typical features which are commonly found in this disorder. The presenting symptoms are usually those of failure to gain weight and grow properly. In the case reported here, however, a urinalysis, which was done in the newborn nursery, was the factor which prompted investigation of the condition. Hepatomegaly and malnutrition may be the only physical findings. Splenomegaly may be present but is usually not extreme. The presence of nuclear cataracts or associated mental retardation may point to the diagnosis.

Edema may be rather marked, as in the case reported here. Mellinkoff, Roth and MacLaggan[14] have recently reported the occurrence of both ascites and peripheral edema in a patient with this disease.

The laboratory findings are those which might be expected in any case of severe liver disease with the additional findings of galactose intolerance. Galactosuria and albuminuria are consistently present while a lactose-containing formula is being ingested. Evidence

of liver damage may be present in the form of prolonged prothrombin time, a decrease in the plasma proteins, abnormal bromsulphalein retention, positive direct van den Bergh test and positive cephalin flocculation or thymol turbidity tests. High levels of reducing substances are found in the blood, the greater part of which is due to galactose. An oral galactose tolerance test results in a high prolonged curve of nonfermentable reducing substance (galactose), accompanied by a simultaneous fall in the fermentable reducing substance (glucose). This reciprocal relationship between blood galactose and glucose was not noted by Bell et al.[2] in their intravenous galactose tolerance test. Bruck and Rapoport[15] theorized that the mutually antagonistic effects of galactose and glucose might be explained by assuming that the two sugars act in a competitive manner on a common metabolic mechanism in the liver.

Normal glucose, adrenalin and insulin tolerance curves are present in this condition when the patient is on a lactose-free diet. The glucose tolerance curve is high and prolonged when on a cow's milk diet, however, due to the large amount of galactose in the serum. The presence of anemia and osteoporosis have been noted by some authors, but are usually not extreme.

The course of a patient with this disease depends upon the age at which the diagnosis is established. If severe liver, kidney and brain damage is allowed to occur, the prognosis is poor. It is apparent from the cases which have been reported, however, that if therapy is instituted early in the course of the disease the pathologic manifestations are reversible. There is usually a prompt weight gain upon elimination of galactose from the diet. Hepatic function is improved and the size of the liver diminishes. The albumin and galactose disappear rapidly from the urine. Increased tolerance to ingested galactose may appear. The cataracts may disappear after several months if therapy is instituted early in life. The presence of cirrhosis of the liver in some cases has been noted by Townsend et al.[13] but the cirrhotic process likewise appears to be reversible. Mental retardation is a common complication, which does not change with other somatic improvement.

The widespread pathologic effects which are found in galactosemia have resulted in considerable speculation. Most authorities agree with Bruck and Rapoport[15] who postulated that the severe manifestations of this disease were toxic in nature and resulted from prolonged high blood galactose levels. Mitchell and Dodge[16] demonstrated the toxic nature of galactose when they found that all rats fed on a ration containing 70% galactose developed cataracts. These cataracts were reversible if the animal was changed to a lactose-free diet sufficiently early.

Discussion

Although their pathologic manifestations differ considerably, the cases which have been presented here have a common denominator. They all present evidence of defective glycogen metabolism which is inborn. The exact pathogenesis of these conditions is still in doubt. Presumably the defect resides in one or more of the complex steps of enzymatic reactions from glucose or galactose to glycogen and its subsequent conversion back to glucose. Different enzyme systems seem to be involved in each entity, however. In addition galactosemia differs from the true glycogen storage diseases in that the liver becomes infiltrated with fat, not a carbohydrate substance.

Bell, Blair, Lindsay and Watson[2] have suggested that the inability to metabolize galactose normally with a resulting fatty liver is comparable to the situation in poorly

controlled human or experimental diabetes where abnormal metabolism of glucose is often associated with fatty infiltration of the liver.

Summary

Five cases have been presented with evidence of disordered glycogen metabolism.

Two cases of glycogen storage disease of the liver are included which were confirmed by biopsy, together with clinical and laboratory evidence. Treatment of one of the cases with adrenocorticotropic hormone resulted in a disappearance of hypoglycemia and acetonuria during the period of therapy.

Two cases of glycogen storage disease of the heart are reported together with clinical histories and necropsy reports. An ECG which was recorded on one of the patients is included.

A case of galactosemia is reported together with extensive laboratory evidence of marked galactose intolerance.

The criteria for the diagnosis of these entities are reviewed and the symptomatology, physical findings, treatment, prognosis and pathologic manifestations are discussed.

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The authors were greatly aided in this study by Miss Grace Lawrence, who did the laboratory determinations, and by Donald Johns, M.D., who participated in the special studies of galactosemia.

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SPANISH ABSTRACT

Alteraciones del Metabolismo del Glicogeno con Refe Rencia en Especial a la Enfermedad por Acumulacion de Glicogeno y Galactosemia

Los autores presentan cinco casos de alteraciones del metabolismo del glicógeno; dos con enfermedad por acumulación de dicha substancia en el hígado que fueron confirmados por biopsia, además de la clínica y el laboratorio y cuyo tratamiento, con hormona adrenocorticotrópica, en uno de ellos produjo la desaparición de la hipoglicemia y acetonuria durante el período terapeútico.

El criterio diagnostico de estos casos lo integran la gran hepatomegalia, desarrollo rápido de hipoglicemia y acetonuria cuando se suspende el alimento, respuesta subnormal o ausencia de respuesta del nivel sanguíneo del azúcar a la inyección subcutanea de adrenalina y al demonstración química o histoquímica de gran cantidad de glicógeno en el hígado.

Dos casos mas de enfermedad glicogénica del corazón con sus historias clínicas y sus informes de autopsia; en uno de estos enfermos se informa su electrocardiograma. Se exige para el diagnóstico de estos cuadros la presencia de cardiomegalia acentuada, muerte dentro del primer año de la vida e infiltración masiva de todas las fibras cardiacas de una substancia que química o histoquímicamente se demuestre ser glicógeno. El último caso fué de galactosemia, en el cual el laboratorio demostró ampliamente la presencia de intolerancia marcada a la galactosa. Hacen una revisión del criterio diagnóstico de estas entidades patológicas y discuten la sintomatología, los datos de exploración física, tratamiento, pronóstico y las manifestaciones anatomopatológicas.

Aunque las manifestaciones patológicas de los enfermos difirieron considerablemente, tenían un denominador comun ya que todos presentaron pruebas de un defecto innato del metabolismo del glicógeno. La patogénesis exacta de estos trastornos es aun dudosa, pero se supone que el defecto reside en uno o mas de los complejos pasos de las reacciones enzimáticas por medio de las cuales se transforma la glucosa o galactosa en glicógeno y éste subsecuentemente se convierte de nuevo en glucosa. Sin embargo, parece que encada entidad estan afectados diferentes sistemas enzimáticos. Además, la galactosemia difiere de la verdadera enfermedad glicogénica por almacenamiento en que el hígado se infiltra con grasa y no con substancias hidrocarbonadas. Algunos autores han sugerido que la incapacidad para metabolizar la galactosa normalmente lo cual produce un hígado graso es comparable a la de los casos de diabetes humana o experimental incompletamente controlados en los cuales se asocia frecuentemente la infiltración grasosa del hígado al metabolismo anormal de la glucosa.

707 Fullerton Street

USE OF BCG VACCINE IN A NEW DIAGNOSTIC TEST FOR TUBERCULOSIS

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CALMETTE and Guérin[1] in 1908 reported the successful cultivation of a nonvirulent strain of bovine tubercle bacillus, which is now universally known as BCG (Bacille Calmette-Guérin). Since then the literature has been flooded with articles concerning the use of BCG as a vaccine in the prophylaxis of tuberculosis. The present communication reports on the value of BCG vaccine* as a diagnostic aid in tuberculosis.

The tuberculin test, as used at the present time, is of inestimable value both for epidemiologic studies and in the diagnosis of tuberculosis. However, its value is lessened by the fact that at times it lacks sensitivity and in other instances it lacks specificity. Thus, in known tuberculous infections it is fairly common to obtain a negative reaction because of a minimum of tuberculin skin allergy. For example, one sees negative tuberculin reactions occasionally in cachectic and even noncachectic tuberculous-infected individuals.

The lack of specificity is noted in the occasional occurrence of "false positive" reactions in noninfected individuals when doses of 1 mg. or more of O.T. (or equivalent doses of P.P.D.) are used in tuberculin testing. Modifications in the technic of the tuberculin test have not completely eliminated these objections.

It is obvious that the value of the tuberculin test would be greatly enhanced if a supplementary test was available which was relatively free from nonspecific reactions, and more sensitive in detecting infected individuals in whom there is a fading or a lack of skin sensitivity to tuberculin.

Numerous observers have noticed that the reaction to the intradermal or cutaneous application of BCG differed in infected and noninfected individuals. Following BCG vaccination of tuberculin-negative, uninfected persons, using the cutaneous multiple puncture method of Rosenthal or Birkhaug, one sees papules appearing after 12 to 20 days.

On the other hand, according to reports from several investigators,[2-10] it is known that when tuberculin-positive individuals are vaccinated with BCG, the local reaction takes place earlier, even on the first and second day. This early reaction also occurs in previously BCG-vaccinated individuals despite the fact that they may be tuberculin-negative. This latter group demonstrates a state of partial hypersensitivity which has been called "infratuberculin allergy" and indicates that allergy to tuberculin has faded; whereas, allergy or immunity to the bacillary proteins or bodies has persisted.

This variation in reaction can be explained by referring to a well known immunologic phenomenon. If an antigen is introduced into the tissue, there is a resultant production of antibodies. The antibody titer gradually falls to zero if there is no further contact with the antigen. Introduce the antigen again and the antibody titer rises once more, though at a much faster rate than on the original introduction of antigen. This is known

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* The BCG vaccine used in this study was supplied by the Research Foundation Tice Laboratory, through the courtesy of Sol Roy Rosenthal, M.D., Medical Director.

as the "anamnestic reaction." It is perhaps most clearly demonstrated in the smallpox vaccination, where a more rapid local reaction takes place in a revaccinated individual than in a previously unvaccinated person. The "Koch phenomenon" is another example of the same mechanism. Koch[11] in 1891 showed that if a guinea pig is infected with tubercle bacilli, a nodule forms by the end of two weeks; chronic ulceration follows with enlarged and caseous regional lymph nodes. On the other hand, if one introduces the living bacilli to a previously infected subject, the local inflammation takes place in two or three days without lymphadenopathy. An ulcer forms in the following days which heals spontaneously. This same reaction may be elicited by dead bacilli and tuberculin.

It is obvious from these observations that the above reaction should be valuable in detecting previous infections with tuberculosis by observing the response of human beings to artificial infection with a nonvirulent, living tuberculosis bacteria, i.e., Bacillus Calmette-Guérin. A few investigators have already utilized the above facts and made studies using BCG as a diagnostic substance.

Thus, Bueno[12] reports that Assis, of the National Department of Health in Brazil, has been using killed BCG since 1942 for an intradermal diagnostic test to determine the presence of infra-tuberculin allergy. Bueno himself, using the same technic, always tests for "infra-tuberculin allergy" before BCG vaccination even in persons who show a negative Mantoux test with as high as 10 mg. O.T. Because of the tendency to ulceration and scar formation with the intradermal technic, Ustvedt and Aanonsen[13] in 1948 introduced their "BCG diagnostic test," utilizing BCG with a skin puncture method. These authors mention five severely ill patients with pulmonary tuberculosis who had negative Pirquet and Mantoux tests, yet a positive early reaction to BCG. Frappier and Guy[14] perform the test by making a single scratch through a drop of live or killed BCG in a manner similar to the von Pirquet tuberculin test.

Frappier has suggested that the BCG test, besides detecting weak or infra-tuberculin allergy, may also act as a booster dose, bringing the faded tuberculin allergy and resistance up to positivity in these cases. In practice Frappier vaccinates immediately with BCG individuals showing a reaction of 2 mm. or less to the BCG test, as he feels that their low degree of allergy corresponds with a poor degree of bacillary impregnation. He reports that no unduly severe reactions were seen in this vaccinated group.

In order to help bring this new diagnostic test to the attention of American physicians, the authors have carried out a small scale study on this subject at the suggestion of Dr. Harold S. Barrett of the Division of Tuberculosis, United States Public Health Service, and Dr. Sol R. Rosenthal.

Materials and Methods

All tests in this study were performed on children aged 4 to 12 yr., residing at the Prendergast Preventorium in Mattapan, Mass.

The BCG vaccine was used in a concentration of 15 mg./cc. The O.T. tuberculin for intracutaneous tests was obtained from the Massachusetts Department of Public Health.

Ninety-one children were tested by means of the Mantoux (intracutaneous) method using O.T. in a dilution of 1:10,000 (.01 mg.). Those who reacted negatively were then retested with a dilution of 1:100 (1 mg.). The tests were read in 48 and 72 hr. and those showing the characteristic redness and induration of 10 mm. or more in diameter after 72 hr. were considered positive.

The same children were then retested with the modified Trambusti method of Ustvedt and Aanonsen, using BCG vaccine instead of tuberculin. The midvolar surface of the forearm was prepared with acetone and a drop of BCG vaccine applied. The vaccine was spread out on the skin so that 2 punctures at least 1½ cm. apart could be made through it. Sterile needles of the type used for smallpox vaccination were found to be satisfactory. When done properly, a small pinpoint hemor-

rhage was noted at the site of the puncture. The vaccine was allowed to dry on the arm. The tests were read daily for the 1st 7 days and again on the 21st day. A distinct papule about 2 mm. in diameter or larger still present on the 8th day, was considered to be a positive, specific "early reaction" to BCG. Papules appearing after 12 to 20 days are called "primary late reaction," to denote the response of a tuberculin-negative, not previously infected individual, to the BCG vaccine. This latter reaction is, of course, similar to the result seen in tuberculin-negative persons who have been BCG-vaccinated with the multiple puncture method of Rosenthal or Birkhaug.

In practice the tests need be read only on the sixth day to detect the positive reactors. It is probably wise to observe the negative reactors once more on the 21st day so that an occasional nontake would be retested. Actually all the "nontakes" were in the Mantoux-negative group so that it may eventually be proved that the reading on the 21st day is unnecessary.

Results

Of the 91 children tested 39 had a positive Mantoux test to O.T. in a dilution of 1:10,000. Two children were positive when the dose of tuberculin was increased to a

GROUP I. MANTOUX POSITIVE

	No. Tested	Early reac. to BCG	Late Primary Reac. BCG	No React.
Mantoux Positive 1:10,000	39	39	0	0
Mantoux neg.—1:10,000 pos.—1:100	2	2	0	0
GROUP II. MANTOUX NEGATIVE				
Mantoux neg. 1:10,000 1:100	46	0	38	8
Mantoux false Pos.—1:100 (faded in 48–72 hr.)	4	0	4	0

dilution of 1:100 (1 mg.). The BCG diagnostic test on these 41 positive tuberculin reactors elicited clearcut papules at least 2 mm. in diameter appearing during the first six days and characteristic of the "early reaction."

Of the remaining 50 children, 46 showed negative Mantoux tests using O.T. in concentrations up to 1:100. BCG diagnostic tests on 38 of this group gave uniformly "primary late reactions." Eight children had no reaction with BCG whatsoever, possibly because of a failure to take. Four of these 50 children showed a false positive reaction to old tuberculin in a concentration of 1:100. Though the reactions faded after 48 to 72 hours, they could conceivably have caused difficulty in interpretation if it had not been for the corroborating "primary late reaction" of the BCG diagnostic test which placed them in the tuberculin-negative group.

The "early reaction" papules appeared within 24 to 48 hours after inoculation. By the sixth day the average induration was 5 mm. in diameter. In the center of the induration there was a spot of necrosis which appeared on the fifth day. In seven of the cases

the necrotic area became a pustule, later forming a small ulcer which, in all cases, was healed by the third week. There were no febrile reactions.

In the tuberculin-negative group there was a slight traumatic redness at the site of BCG injections, which cleared in one or two days. When examined at the end of three weeks, these children developed raised red papules from 1 to 3 mm. in diameter at the inoculation site (primary late reaction).

Thirty-four of the 50 children who were classed as tuberculin-negative on the basis of the BCG and Mantoux tests were retested one year later. All 34 remained negative to both tests, indicating that the amount of BCG used in doing the test is usually not sufficient to convert a negative reactor into a positive one.

Comments

With present-day interest in BCG mounting, there is a corresponding increase in the need for accurate determination of which individuals require prophylaxis.

Long before Paretzky[15] in 1936 collected 80 revertors, it was known in Europe that positive tuberculin reactions often reverted to negative. The BCG test apparently detects "infratuberculin allergy" in many of these revertors and raises the important point as to whether these individuals have sufficient immunity to tuberculosis or whether further stimulation in the form of BCG vaccination is necessary. This is especially true in BCG-vaccinated individuals who remain tuberculin-negative. Are further vaccinations necessary or does an early reaction to BCG indicate sufficient immunity in these subjects? Only long term follow-up studies will settle this question.

In this series the authors have encountered no cases of "infratuberculin allergy," i.e., early reaction to BCG in subjects negative to tuberculin. This is understandable since such a state is not so common in young children with the natural infection who are in good condition. However, Ustvedt and Frappier, dealing with older individuals, encountered a good many such cases.

As far as the safety of the test is concerned, the reports of millions of BCG vaccinations without a fatality bears some evidence to the lack of danger in this procedure. Scholer[16] in Switzerland reports performing the test with live BCG in a strength of 75 mg./cc. and had no ill effects. The BCG used in the authors' tests had a strength of only 15 mg./cc. A search of the literature reveals not a single record of any serious result from BCG vaccination of individuals with tuberculous lesions, unless these are far advanced, and a report by John Bøe[17] reviews much of the literature indicating that BCG inoculations do not harm individuals infected with tuberculosis.

At the present time the authors are working with killed BCG and it appears so far that the results are similar to those obtained with live BCG. This modification, if further investigation proves its feasibility, should further allay any fears concerning the use of this test.

Summary

Ninety-one children were Mantoux-tested using O.T. in a dilution of 1:10,000 (.01 mg.). Negative reactors were retested with a 1:100 (1.0 mg.) solution of O.T.

All the children were then tested by making two punctures through a drop of BCG vaccine applied to the arm. The Mantoux-positive group developed papules during the first six days after inoculation with BCG. The tuberculin-negative individuals showed a late reaction to BCG in 12 to 20 days, similar to that seen in tuberculosis uninfected

individuals when BCG vaccinated by the method of Rosenthal or Birkhaug. In four cases false "positives" were elicited with O.T. These were easily differentiated by the demonstration of a late reaction with the BCG test. Thirty-four of the negative reactors were rechecked one year later and showed no change in their status as a result of the BCG test.

It is true, of course, that the number of children studied in this series is too small to justify any final conclusions about the role of BCG in routine tuberculin testing. The authors feel, however, that the findings together with the findings of other investigators indicate that BCG vaccine is a more sensitive and more specific test than the ordinary tuberculin test and it therefore should be of value in the following situations:

1. Where the authenticity of a "positive tuberculin test" is doubted.
2. In cases of tuberculin anergy where clinical evidence seems to indicate tuberculous infection despite a negative tuberculin test.
3. To detect infratuberculin allergy when BCG vaccination is contemplated. Further research is necessary to determine whether BCG vaccination is necessary in the presence of infratuberculin allergy.

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Spanish Abstract

Uso del BCG como una Nueva Prueba para el Diagnostico de la Tuberculosis

Los autores llaman la atención a la frecuencia en que la prueba de la tuberculina resulta negativa en presencia de una infección tuberculosa. Otras veces la misma prueba de tuberculina resulta en una

reacción pseudopositiva en individuos jamás infectado con tuberculosis. Es decir, que la prueba de la tuberculina tal como ordinariamente es hecha con tuberculina vieja, frecuentemente carece de sensitividad y otras veces le falta especificidad.

Se recomienda el uso del BCG como una prueba mas sensitiva y especifica para el diagnóstico de la tuberculosis. Los autores recomiendan su aplicación como una prueba suplementaria en todos aquellos casos donde los resultados obtenidos con la prueba de tuberculina ordinaria sean dudosos, ó no se ajusten al cuadro clinico del enfermo. Esta prueba se basa en el fenomeno de Koch, y se realiza haciendo un pinchazo en la piel atráves de una gota de la vacuna BCG.

416 Marlborough Street

CHRONIC HEMOLYTIC ANEMIA IN A WHITE CHILD DUE TO THALASSEMIA AND SICKLEMIA

With a Genealogic Survey

By CHARLES F. WASSERMAN, M.D., V. RAE PHELPS, PH.D., AND A. J. HERTZOG, M.D.
New Orleans

CHRONIC hemolytic anemia due to thalassemia and sicklemia was first reported in the United States by Powell, Rodarte and Neel[1] in 1950. They demonstrated that in their patient's pedigree the gene responsible for sickling was inherited through one side of the family and that for thalassemia through the other, resulting in an individual who possessed both of these genes in the heterozygous state. Eight similar cases have been reported from Italy.[2-4]

In the present authors' case, the second example of this phenomenon to be reported from the United States, an ostensibly white girl has inherited the thalassemia gene from her father, the sickling gene from her mother, and has severe chronic hemolytic anemia.

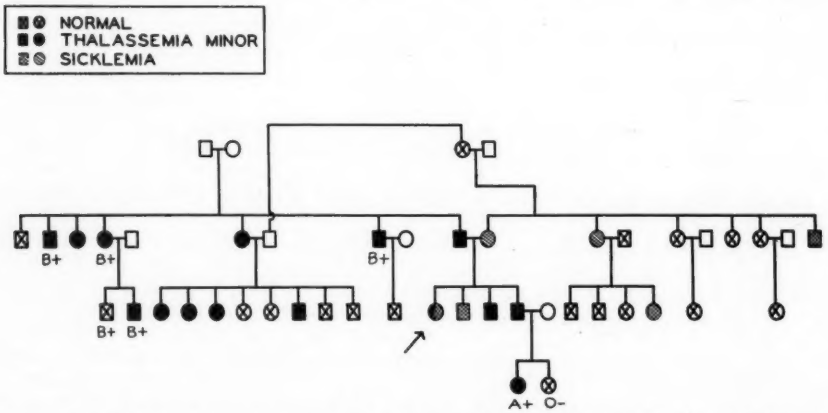

CHART 1. Genealogic chart to show pattern of inheritance for blood groups, sicklemia and thalassemia traits. Unless specifically indicated, patient's blood group is type O, Rh-positive (D).

This 8 year old white girl of apparently pure Sicilian descent (with no known Negro ancestry) has had multiple episodes of polyarthralgia, fever, malaise, pallor, abdominal pain and mild jaundice for the past four years. Repeated examinations have always revealed a chronically ill child, usually mildly jaundiced and pale. Temperature and respiratory rate have usually been normal but there has been a persistent slight tachycardia. There has always been a harsh, blowing systolic murmur over the entire precordium,

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loudest at the apex. The spleen has been palpable about 5 to 6 cm. below the costal border.

Roentgenographic studies of the heart have given the appearance of generalized enlargement, and films of the long bones and skull have shown no abnormalities. Repeated electrocardiograms have been interpreted as normal.

The initial complete peripheral blood study at the age of 4 years was as follows:

Hematocrit	27
Total RBC's	3.9 million/cmm.
Reticulocytes	10.6%
Hgb.	6.9 gm. (44%)
Color Index	0.56
Total WBC's	16.0 thousand/cmm.
Neutrophils	40%
Eosinophils	2%
Lymphocytes	52%
Monocytes	6%
M.C.V.	68μ
M.C.H.	17 γ
M.C.H.C.	25%

Smears showed marked hypochromasia, polychromatophilia, and many "target cells."
Sickling preparation was positive.
Fragility test:
Patient—0.40, not complete at 0.24
Control—0.42-0.30
Sternal marrow was normoblastic with erythroid hyperplasia.

The child has had numerous admissions for recurrent episodes of anemia over the past four years, and to date has received 18 transfusions. At present she seems to require blood transfusions of 500 cc. approximately every 12 weeks in order to maintain a hemoglobin level of 10 gm. or more, and to relieve symptoms of fatigue which seem obvious below that level.

The child's hematologic picture has been that of a chronic recurrent hemolytic anemia with characteristics of both thalassemia minor and sicklemia. Repeated studies have shown no remarkable changes from that described above, aside from variations in the degree of anemia.

Examinations, including complete peripheral blood studies, fragility tests, blood typing and sickling preparations were recently carried out on 37 relatives in three generations, and the pertinent results appear in figure 1. The thalassemia gene is limited to the paternal side of the pedigree, while the sickling gene is confined to the maternal side. In the sibship of the propositus, there are two males exhibiting typical features of thalassemia minor while a third brother, who died at the age of four years following an appendectomy, was found to have sicklemia on the basis of postmortem studies, and may or may not have also exhibited thalassemia minor. He died suddenly following the laparotomy. In retrospect, one might theorize that in view of his recurrent abdominal pains, with a normal appendix and sicklemia, he might have had a sickle cell crisis or possibly even this plus thalassemia minor.

Four theories have been proposed to explain this disease.[1] Two of these propose that the clinical picture is due solely to one of the two factors, while the other two theories have as their bases the genetic interaction of both factors. It is at least theoretically possible

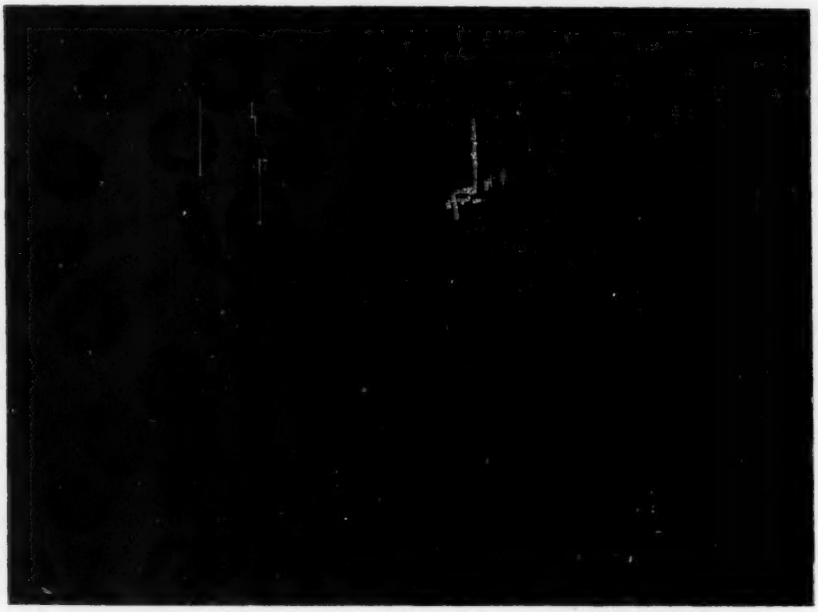

FIG. 1

Photomicrograph of blood smear, demonstrating sickle cells as well as target cells.

that the heterozygous condition of the sickling gene might alone account for the symptoms, thalassemia being incidental; this is unlikely, however, since a severe clinical picture in an individual who is heterozygous for the sickling gene has never been recorded. Another possibility would be the converse of the above theory, namely, that the thalassemia gene is responsible for the anemia and that sickling is incidental. While a mild anemia occasionally occurs in thalassemia minor, it is not as severe as in the patient reported here.

In the light of our present knowledge concerning inheritance of sicklemia and thalassemia minor as separate conditions, two genetic theories may be proposed to explain the severe clinical manifestations in individuals having both. If the sickling and thalassemia genes are inherited as two independent Mendelian factors, then the child in this pedigree represents a double heterozygote. The genotype could be the result of retrograde heterosis. Here the two abnormal factors, each by itself resulting in only a mild expression, in combination augment one another (perhaps either by biochemical interaction or mutual interference) to such an extent that a more severe clinical syndrome results. This theory seems the most plausible one to the authors. The last genetic explanation supposes that the sickling and thalassemia genes are both mutations from an original normal gene, and thus constitute a series of multiple alleles with the normal gene. In that case this patient would represent a heterozygote of two abnormal genes, and because of the absence of any normal allele and the augmentation effect of the actions of these two genes, could be expected to exhibit severe clinical manifestations.

Although the pattern of retrograde heterosis has been recognized for some time in experimental genetics, the phenomenon has not yet been adequately studied and has been

largely ignored in clinical medicine. While it is accepted that one disease entity may aggravate or increase the severity of another, the concept of two independently inherited conditions producing, by the summed action of the two different alleles, one clinical syndrome possessing characteristics that neither gene may produce alone or would otherwise be expected to produce in combination, is a field of investigation which deserves more attention. Also, therapy which may be indicated for either one of the conditions when they occur separately may be necessarily more diligent.

Proof as to which of the genetic theories is the correct one must await the collection of a larger number of such cases, with adequate familial studies together with cases in which such a severely affected individual has produced children. If the multiple allele theory is correct, then such a person could never produce a normal child regardless of the status of a marriage partner, since all the children would have inherited either the sickling or the thalassemia gene from one parent. Therefore the production of a normal child by a severely affected individual would disprove the multiple allele theory and substantiate that of two independently inherited factors. Positive proof of the multiple allele theory, on the other hand, would be more difficult since it would require study of many offspring of a severely affected parent to demonstrate a statistically significant dearth of normal children.

Summary

The authors have described the second case in the United States of chronic hemolytic anemia resulting from the genetic factors for sicklemia and thalassemia minor in combination. A complete hematologic study of 37 relatives of the propositus is presented. The four possible theories, as proposed by earlier investigators, which may explain the severe clinical manifestations, are given.

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Spanish Abstract

Anemia Hemolítica Crónica en un Niño Blanco como Resultado de la Siclemia y Tendencia a Anemia de Cooley

Hemos descrito el segundo caso encontrado en los Estados Unidos de la anemia hemolítica crónica como resultado de una fisión de los factores genesíacos de la siclemia y tendencia a anemia de cooley. Se presenta un estudio hematológico en completo de 37 personas emparentadas con la enferma. Hay una posibilidad de 4 teorías sugeridas por investigadores anteriores, que son capaces de explicar los graves síntomas hallados.

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EXOGENOUS HEMOCHROMATOSIS IN MEDITERRANEAN ANEMIA

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EVIDENCES of generalized pigment deposition have always been of clinical importance in Mediterranean anemia. The previous medical literature has ascribed these findings to an inherited defect which was also held responsible for the hematologic manifestations of this disease.[1] The authors have recently observed a moderately severe form of Mediterranean anemia in a patient who had received 76,665 cc. of blood over a period of 9 years. The case is reported to support the opinion that the abnormal pigment deposition in Mediterranean anemia is due to repeated blood transfusions rather than an inherited defect, these cases being but additional examples of exogenous hemochromatosis.

CASE REPORT

J. F., a 6 mo. old female of Italian parentage, was admitted to the Pediatric Service of the Mt. Sinai Hospital for the diagnosis and treatment of an anemia of undetermined origin. Physical examination was essentially negative except for a severe degree of pallor, questionable scleral icterus, and a spleen enlarged 2 to 3 finger breadths below the left costal margin. A blood count showed: RBC 2.5 million/cmm., Hgb. 6.7 gm./100 cc. (46%), reticulocytes 9.4%, platelets 220,000/cmm., WBC 11.0 thousand/cmm. with 1% myelocytes, 1% metamyelocytes, 12% bands, 58% segmented, 20% lymphocytes, 4% monocytes, 3% eosinophiles, 1% basophiles. The smear showed marked aniso cytosis and poikilocytosis. Hypochromia was especially prominent. The usual orthochromatic target cells, oval cells and basophilic stippled erythrocytes seen in Mediterranean anemia were present. In addition, 70 nucleated RBC/100 WBC were counted. Smears of aspirated marrow showed normoblastic hyperplasia. The icterus index was 6.9. RGs of the bones were interpreted as normal. A diagnosis of Mediterranean anemia was made.

During the following months, the child was readmitted for supportive blood transfusions. At approximately one year of age, she was readmitted for further evaluation and treatment. At that time there was a marked degree of pallor and a definite scleral icterus. The liver was enlarged 2 finger breadths below the right costal margin and the spleen was palpable 3 finger breadths below the left costal margin.

Multiple transfusions were given until satisfactory values for the RBC count and hemoglobin were attained. A splenectomy was then performed. Although this relieved the infant of the burden of a large spleen, it had no apparent effect on the hemolytic process. The values for the erythrocytes and hemoglobin soon returned to their previous low levels.

In the succeeding years the child was followed in the outpatient department. Blood transfusions were given when either RBC count had fallen below 3 million or Hgb. below 9 gm. Approximately 450 transfusions totalling 76,665 cc. were given over a period of 9 yr. (table 1). A gradual pigmentation of the skin was noted to develop. All the accepted hematinics—iron, parenteral liver extract, folic acid and B12—were tried at one time or another and then discontinued because of lack of favorable response.

At 10 yr. of age the child was readmitted for further evaluation. She was active and alert, but was smaller than average and had very little subcutaneous fat. There was a peculiar, slate gray pigmentation of the skin, particularly marked over the face and hands. The skull was not abnormal in appearance. The conjunctivae were pale and definite scleral icterus was present. A systolic murmur

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TABLE 1

	Amount of Blood Transfused Each Year
1940	2,750 cc.
1941	4,210 cc.
1942	7,120 cc.
1943	4,125 cc.
1944	6,260 cc.
1945	8,400 cc.
1946	5,050 cc.
1947	9,500 cc.
1948	12,000 cc.
1949	14,500 cc.
1950	2,750 cc.
Total	76,665 cc.

was heard over the pulmonic area. The scar of the previous splenectomy was noted in the left upper quadrant. The liver was enlarged 5 finger breadths below the right costal margin. Its edge was smooth, nontender and moved freely with respiration. The remainder of the physical examination was entirely normal.

A survey of the more important studies done at this time follows: The patient's red cells began to hemolyze at 0.42% NaCl and hemolysis was not completed till 0.14% concentration was reached. Hemolysis began, for the control, at 0.46% and ended at 0.32% NaCl solutions. A fecal urobilinogen excretion of 188 mg./day was found. An *in vivo* test for hemosiderin deposition in the skin[2] was negative. A skin biopsy was reported by the pathologist as follows: "Sections of skin stained with hematoxylin and eosin are essentially normal. The sections, when stained with potassium ferrocyanide (iron stain), revealed a positive reaction. This is most marked in the corium, particularly about the sweat glands. Adequate positive and negative control sections were done." Bromsulfalein retention: 4 min. 54%, 30 min. 3%, 45 min. 1%; alkaline phosphatase 14.2 Bodansky units; prothrombin time-normal; cephalin flocculation test—negative; thymol turbidity—4.5; a capillary glucose tolerance test showed: fasting 101 mg./100 cc., ½ hr. 154 mg./100 cc., 1 hr. 167 mg./100 cc., 2 hr. 138 mg./100 cc., 3 hr. 110 mg./100 cc. Dilated esophageal varices were not demonstrated by RG. The medullary trabeculae in the long bones were not prominent. The skull has a "washed out" appearance by RG.

TABLE 2

Blood Counts of Patient and Family Members with Trait

	Patient	Father	Mother	Sister
RBC	1.92 M	4.40 M	3.89 M	3.82 M
Hgb.	5.9 M	13.0 gm.	10.5 gm.	12.0 gm.
Reticulocytes	4.5%	4.2%	3.7%	2.2%
Platelets	310,000	350,000	390,000	300,000
WBC	16,500	8,100	8,800	8,800
Myelocyte	2			
Metamyelocyte	5			
Band	11	6	5	3
Segmented	36	52	57	62
Lymphocyte	38	34	32	29
Monocyte	5	5	5	2
Eosinophile	2	2	1	4
Basophile	1	1		
Nucleated RBC/100 WBC	250			

A study of the patient's family revealed that both parents had the Mediterranean trait (table 2). In addition the mother stated that one of her sister's children had died with "Cooley's anemia." A study of the children revealed that one sister had the trait and the remaining half-sister and brother did not.

Shortly after these studies were completed the child was admitted to the Pediatric Ward in cardiac failure. Despite transfusions of whole blood, mercurial diuretics, digitalis and oxygen therapy, the patient failed to respond and died in congestive failure.

The autopsy findings are restricted to those organs of particular importance to this case. Marked, gross, brownish pigmentation particularly of the liver, pancreas and lymph nodes was seen. Microscopic sections revealed extensive hemosiderin deposition in the liver, pancreas, lymph nodes, cardiac muscle, gastric mucosa, renal tubules, sweat glands of the skin, and zona glomerulosa of the adrenal glands. In addition, the microscopic features of an early, active portal cirrhosis were seen.

Discussion

This development of exogenous hemochromatosis in the patient was most interesting. Over many years she gradually developed a peculiar pigmentation of the skin. This was usually described as "dirty" or "slate gray" in color. It was most marked over the exposed portions of the body, i.e., face, hands and feet. The presence of marked hepatomegaly associated with these skin changes focused attention to a possible developing hemochromatosis.

The pathologic features of Mediterranean anemia were completely described by Whipple and Bradford in 1936.[1] The features of pigment deposition were likewise noted in their cases. However, they attributed these findings to Mediterranean anemia itself, rather than to the repeated blood transfusions. They stated, "The pigment abnormalities are conspicuous in this disease and follow accurately the pattern of pigment distribution in hemochromatosis. . . . The disease (i.e., Thalassemia) is due to some racial, inherited defect which is responsible for the abnormality of the hematopoietic tissue, the bone changes . . . and the pigment abnormalities (practically identical with hemochromatosis). . . . We believe the pigment deposits in these cases (simulating hemochromatosis) are as characteristic of this disease as are the recorded abnormalities of the hematopoietic system and bony skeleton. . . . The pattern of pigment distribution in hemochromatosis and thalassemia is almost identical; therefore the inevitable conclusion follows that the blood disturbance probably is not responsible for the pigment abnormalities in thalassemia." Their opinion that the pigment deposition was due to some inherited defect rather than repeated blood transfusions undoubtedly led to the nonrecognition of exogenous hemochromatosis in other individuals with Mediterranean anemia.

The syndrome of exogenous hemochromatosis, following repeated blood transfusions, was first described by Schwartz and Blumenthal.[3] They collected five such cases, added eight more from the medical literature,[4–9] and described the condition for which they suggested the term "exogenous hemochromatosis." Analysis of their cases revealed diabetes to be present in two, skin changes in five, enlargement of the liver in nine, hemosiderosis and fibrosis of the liver, pancreas, etc., in 12. More instances have since been reported[10–12] in anemias of various types and etiologies. The common denominator in all was the history of multiple blood transfusions.

The patients with Mediterranean anemia had similarly received many blood transfusions. It would therefore appear that the pigment deposition in Mediterranean anemia is due to multiple blood transfusions rather than a postulated inherited defect. This concept is further strengthened by the absence of such pigment deposition in individuals with Mediterranean trait. In these cases the anemia was of such a mild nature that blood

transfusions were not required. These patients therefore failed to develop pigment deposition as seen in exogenous hemochromatosis.

Summary

A patient with Mediterranean anemia who received many blood transfusions over a period of years is presented.

The pigment deposition in Mediterranean anemia, originally thought due to an inherited defect, is attributed to multiple blood transfusions.

It is maintained that this abnormal pigment deposition represents another instance of exogenous hemochromatosis.

Acknowledgment

The authors wish to acknowledge the assistance of Dr. David R. Meranze, Pathologist and Director, Department of Research, Mt. Sinai Hospital, in the preparation of this manuscript. The authors also wish to thank Miss Helen Gordon for her careful blood studies.

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Spanish Abstract

Hemocromatosis Exógena en la Anemia Mediterranea

Los autores describen un paciente con anemia Mediterranea de severidad moderada, él cual recibió numerosas transfusiones de sangre durante un período de varios años. Sé confirmó el fracaso de la esplenectomía en modificar el curso de la enfermedad. Sé observó un aumento en la pigmentación de la piel y hepatomegalia progresiva con el transcurso de los años. El diagnóstico de hemocromatosis exógena fué hecho en éste paciente. Sé observó que a pesar de la presencia de alteraciones microscopicas severas del párenquima hepatico, los estudios de la función hepatica de éste paciente resultaron esencialmente normales. Se revisan las características patológicas de la deposición anormal de pigmentos en la anemia Mediterranea, las cuales conjuntamente con las alteraciones hematologicas y óseas se

estimaba eran debidas a un defecto hereditario. Sé encontró que la deposición de pigmentos en la anemia Mediterranea fué similar a la observada en individuos con hemocromatosis exógena. Basandose en esta observación, los autores estiman que la deposición anormal de pigmentos en la anemia Mediterranea es debida a las transfusiones múltiples de sangre que estos pacientes reciben, y no el resultado de un defecto hereditario como previamente se creia.

Fifth and Reed Streets

OSTEOID OSTEOMA IN CHILDHOOD

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OSTEOID osteoma recently has received considerable attention in the surgical, pathologic and orthopedic literature and is now generally accepted as a definite clinical and pathologic entity. However, it is only within the past few years that osteoid osteoma has been generally recognized as being distinct from certain other neoplastic, inflammatory and metabolic lesions of bone. Today, osteoid osteoma is being reported with increasing frequency and since the patients in approximately 40% of the reported cases have been 15 years of age or less,[1] this condition should be familiar to the pediatrician.

Jaffe,[2] in 1935, was the first to use the term "osteoid osteoma" in describing what he believed to be a benign tumor of bone, although others[3-5] thought the condition might be a result of inflammation. In 1941, Mallory[6] stated that the cause of osteoid osteoma was not inflammation because fever was not present, cultures of the pathologic tissue gave negative results and microscopic examination failed to suggest inflammation. In 1945, Jaffe[7] wrote that osteoid osteoma sometimes was confused with certain types of local infection of bone because the roentgenogram in a case of osteoid osteoma might appear similar to that obtained in the presence of local infection of bone but, he continued, clinically there was little resemblance, and anatomically there was no resemblance between osteoid osteoma and bone infection.

Osteoid osteoma is a small, benign tumor of bone and usually of endochondral bone. It has been reported as occurring in every bone of the skeleton except the skull, facial bones and clavicle, but it is most commonly found in the long bones of the extremities.[8] Like other benign tumors, it does not metastasize but will recur if not completely removed. It is typically a single lesion; only two instances of a double lesion have been reported.[1,9] It occurs in a ratio of 2 males to 1 female. Patients usually are in the second decade of life, with a concentration in the early "teens," but cases have been reported in which the patients' ages have ranged from 22 months to 51 years.

The outstanding and frequently the only symptom is pain. This pain is moderate or mild; nevertheless, often it is severe enough to cause the child to cry. However, the pain is intermittent with attacks occurring once or twice a day and continuing for an hour or two each time. Between the attacks, the patient is usually comfortable. The pain frequently is nocturnal, interfering with sleep. It is usually described as "boring" or "like a toothache" and the seat of the pain seems to be within the involved bone. Occasionally, the pain may radiate to a limited extent or involve a nearby joint. Active or passive movement of the part usually does not bring on or accentuate the pain. Administration of salicylates, massage, application of heat, or other measures are not very helpful in relieving the discomfort.

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FIG. 1. Roentgenographic appearance of osteoid osteoma of midshaft of right tibia. Radiolucent area is surrounded by evidence of osteosclerosis.

FIG. 2. Nidus of osteoid osteoma sharply demarcated from surrounding sclerotic bone. (x19; from Jackson, A. E., Osteoid Osteoma, Thesis, University of Minnesota Graduate School, 1948.)

Whereas pain is practically always present, other symptoms are not a uniform part of the disease. The patient may have noticed swelling but for this to be evident the tumor must have evoked some periosteal reaction and the involved bone must be fairly superficial. Swelling, therefore, is more frequently found, for example, if the lesion is in the anterior part of the tibia than if it is in the upper part of the femur. If the lower extremity is involved, a limp is usually present. It may precede or follow the onset of the pain. Tenderness may have been noticed but it is never very marked. One of the major complaints occasionally is of loss of weight and such loss seems to be of more frequent occurrence if the lesion occurs in the pelvic girdle than if it appears elsewhere.

The examining physician may find a hard, fusiform swelling if the lesion is superficial. This is continuous with the shaft of the bone and may be slightly tender. Increased local warmth and redness of the overlying skin occasionally are found. Fever, however, is seldom present and, if found, may be explained by some incidental infectious process. Atrophy is of fairly common occurrence and, if the osteoid osteoma involves an extremity, the atrophy may be associated with muscular weakness and definite depression of the deep tendon reflexes; these signs, on occasion, may suggest a neurologic lesion.

Laboratory data are significant in that they are normal. Elevation of the sedimentation rate and of the leukocyte count is not characteristic of osteoid osteoma. These determinations therefore are helpful in the differential diagnosis of this condition from infectious processes.

The roentgenogram of the involved bone is of great aid but it is not an infallible means of making the diagnosis. Characteristically, there is an area of radiolucency measuring a few millimeters in diameter, surrounded by osteosclerosis measuring several centimeters in diameter (Fig. 1). The zone of rarefaction usually has a fairly well-defined margin, and is the so-called nidus found on pathologic examination. Occasionally, the nidus may be partially calcified and flecks of increased density are seen within the radiolucent area, or the nidus may be almost completely calcified, in which case only a halo of radiolucency surrounds the dense nidus. The extent and intensity of the surrounding osteosclerosis also is variable but the process is usually several times the size of the nidus. Because of this sclerosis, it is frequently necessary to give the film more exposure than normal if the nidus is to be visualized. Also, symptoms may precede demonstrable roentgenographic changes and, occasionally, a typical picture will be found several months after an initial roentgenogram was negative.

The pathologic findings are characteristic and, as was stressed by Jackson[10] and by Dockerty, Ghormley and Jackson,[11] are the only means of arriving at an absolute diagnosis of osteoid osteoma. On gross examination of the involved bone (Fig. 2), a variable area of dense bone is found, within which is the nidus, usually measuring less than 1 cm. in diameter. The nidus, which usually is separated from the surrounding bone by a definite line of cleavage, has the appearance of granulation tissue, being friable and of a reddish-brown color. It may be gritty when cut with a knife because variable amounts of calcium are present. The lesion may be located within the medullary canal, at the margin of the cortex and medullary canal, completely within the cortex or subperiosteally. Microscopically, the nidus is composed of irregular spicules of osteoid tissue which lack the normal lamellar structure of the surrounding sclerotic bone. Variable numbers of giant cell osteoclasts are seen along the spicules in Howship's lacunae. Between the spicules is a matrix composed of fibroblasts and osteoblasts. The osteoid tissue may or may not be calcified. The matrix is highly vascular. Mitotic figures are not increased in number and there are no cells characteristic of inflammation.

Osteoid osteoma must be diagnostically differentiated from several other conditions which produce lesions in bone. Among the most confusing are Brodie's abscess, solitary cortical abscess, small isolated tuberculous abscess and Ewing's tumor. These and others will be considered in the immediately following paragraphs:

1. Brodie's abscess is a chronic, circumscribed focus of pyogenic infection of cancellous bone located at the extremities of the long bones, mainly the upper end of the tibia or lower end of the femur (Fig. 3). It manifests itself as a small cavity surrounded by dense bone which may cause intermittent pain and fusiform enlargement of the bone without much, if any, febrile reaction. Surgical exploration usually reveals pus, bacteriologic culture may give a positive result and microscopic examination of tissues from the lesion discloses evidence of inflammation.

2. A solitary cortical abscess of bone is an infection lying within the cortex. Cortical abscess may occur in conjunction with other lesions of osteomyelitis, but it is confused with osteoid osteoma only when it occurs singly. The age group, symptoms, distribution by sex and febrile reaction do not serve to distinguish cortical abscess from osteoid

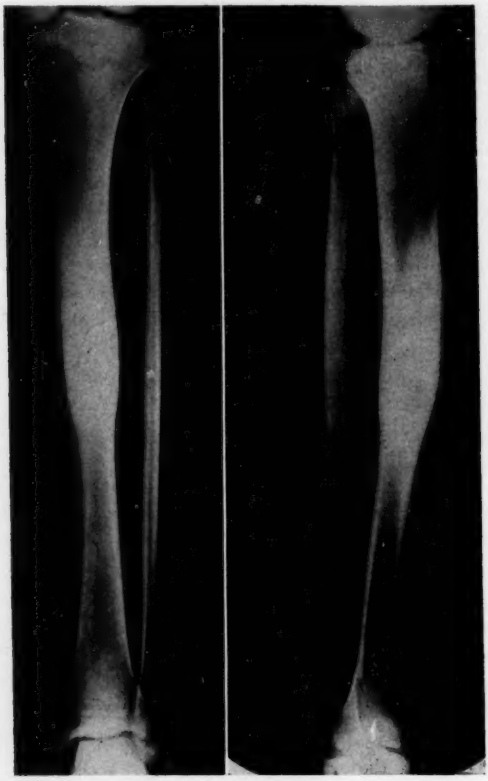

FIG. 3. RGs of left leg. Radiolucent area is surrounded by evidence of osteosclerosis in midshaft of tibia. Although picture resembles that of osteoid osteoma, on examination by pathologist this lesion proved to be Brodie's abscess.

osteoma. However, microscopic examination of tissue from a cortical abscess reveals evidence of chronic inflammation.

3. Chronic sclerosing osteomyelitis of Garré is a nonsuppurative form of infection of bone which produces thickening and distention of the shaft, with some encroachment on the medullary cavity. It usually involves the shafts of the long bones, mainly the tibia and femur. Typically, there is a febrile reaction and sufficient leukocytosis to aid in the diagnosis, but rarely these may be absent. A radiolucent area, similar to that of osteoid osteoma, is not seen and microscopic examination of the bone reveals inflammatory changes. The intense osteosclerosis present in some cases of osteoid osteoma may partially obscure the nidus and render the roentgenogram similar to that of sclerosing osteomyelitis (Fig. 4).

4. A single tuberculous cavity in the shaft of a long bone, an extremely rare condition, occasionally may give an appearance similar to that caused by osteoid osteoma (Fig. 53. The diagnosis rests on culture of the material found in the abscess and on microscopic examination, although a positive tuberculin test and elevation of the temperature and

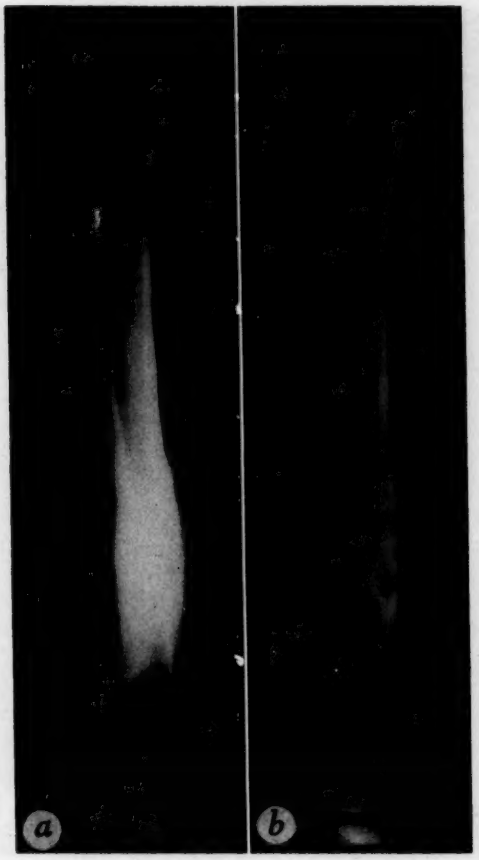

FIG. 4a. Roentgenographic appearance of marked osteosclerosis with thickening of shaft of left tibia. Specimen taken from this region was interpreted as being characteristic only of sclerotic bone and clinical diagnosis was sclerosing osteomyelitis. b. Symptoms persisted and 2 yr. later, with heavier penetration of roentgen rays, nidus was demonstrated. This was removed and was identified by pathologist as osteoid osteoma.

sedimentation rate may be suggestive of the true diagnosis prior to surgical operation.

5. Ewing's tumor occurs typically in the middle third of the shaft of a long bone. The distribution by age and sex and the early symptoms are not remarkably different from those of osteoid osteoma. Since the tumor arises in the marrow cavity and spreads in all directions, the shaft becomes widened. Elevation of the periosteum produces the "onion peel" appearance of the roentgenogram. When the lesion becomes further advanced, the marked destruction of bone makes the diagnosis easier than before. Microscopic examination at any time, of course, reveals the true nature of the lesion. Figure 6 represents a case of osteoid osteoma in which the roentgenographic appearance presented many similarities to that of Ewing's tumor.

6. Osteogenic sarcoma is not difficult to differentiate diagnostically from osteoid

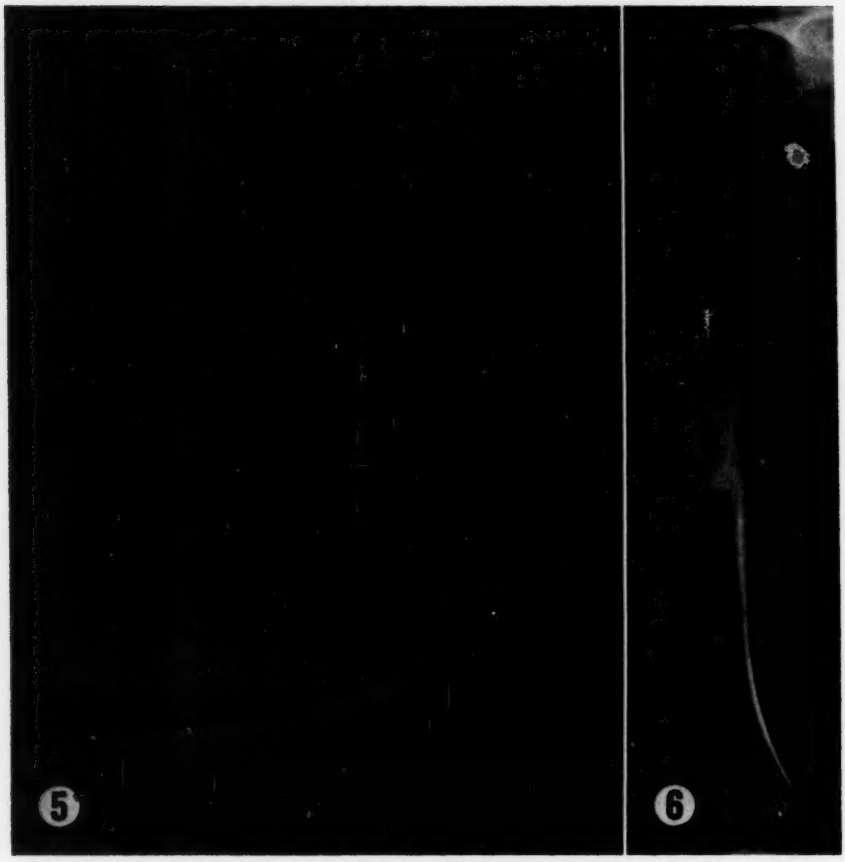

FIG. 5. Roentgenographic appearance of left elbow. Radiolucent area in lower portion of humerus is surrounded by zone indicative of osteosclerosis. Although this lesion presented some roentgenographic similarities to osteoid osteoma, pathologist found it to be tuberculous.

FIG. 6. Roentgenographic appearance of osteoid osteoma involving midshaft of right humerus. Many roentgenographic similarities to Ewing's tumor are apparent.

osteoma when osteogenic sarcoma is associated with considerable destruction of bone and invasion of the surrounding soft tissues, producing the "sun ray" effect seen on the roentgenogram. In an early stage, however, osteogenic sarcoma may be identifiable only by condensation of reacting bone around a small area of bone destruction. The symptoms of pain, tenderness and swelling do not necessarily differ from those of osteoid osteoma, but the rapid progression of osteogenic sarcoma and microscopic examination, of course, make the diagnosis.

7. Fibrous dysplasia, Albright's syndrome, simple bone cyst and hyperparathyroidism present little trouble in differential diagnosis, since pain is not a feature of these lesions and the roentgenograms are not easily mistaken for those of osteoid osteoma.

TABLE 1

AGE AND SEX

Age, yr.	Patients
0– 5	3
6–10	2
11–15	8
	13
Sex	**Patients**
Male	9
Female	4
	13

TABLE 2

Symptoms of osteoid osteoma, 13 patients	
Pain	12
Atrophy	8
Swelling	7
Tenderness	6
Wt. loss	5

TABLE 3

Situation of osteoid osteoma	
Tibia	5
Femur	4
Ulna	2
Humerus	1
Ilium	1
	13

TABLE 4

Roentgenographic findings in 13 cases of osteoid osteoma	
Radiolucent area	13
Osteosclerosis	13
Cortical thickening	10
"Onion peel" appearance	4

SURVEY OF 13 CASES IN WHICH THE PATIENTS WERE CHILDREN

To date, at the Mayo Clinic, osteoid osteoma of children has been proved in 13 cases by pathologic examination of tissues removed at surgical operation. Other cases have seemed typical as far as symptoms, physical findings and roentgenographic studies were concerned, but operation was not performed for one reason or another. Because pathologic confirmation of the diagnosis was lacking, these cases were not included in this study. Of the 13 cases in which the diagnosis was proved, in 9 the patients were males (table 1). The youngest patient was 22 months of age and three were less than the age of 6 years (table 1). There seems to be an increase in frequency around puberty.

Symptoms, signs, situations of the lesions and roentgenographic findings are summarized in the remaining tables. Pain occurred in all but one case (table 2). The one exception was the patient of 22 months, who was brought to the clinic because of a painless swelling on the anterior surface of the tibia. Other manifestations listed in table 2

were inconstant. Most of the lesions were in the long bones of the extremities (table 3). Of the 10 patients whose lesions were in a lower extremity, eight limped. The roentgenographic findings were fairly uniform (table 4).

Each of the 13 patients underwent a surgical procedure to remove the tumor. This consisted, in most cases, of excision of a block of bone containing the nidus. In two cases, the lesion was subperiosteal and the bone was saucerized well beyond the limits of the nidus. Results were uniformly good; virtually complete alleviation of symptoms immediately followed the surgical operation. The shortest follow-up period was three months and the longest, five years. In these periods, there were no relapses. One patient had been operated on for what had been called chronic sclerosing osteomyelitis. However, symptoms persisted and on a second examination, two years later, the nidus of osteoid osteoma was demonstrated. This was excised and symptoms were completely alleviated. The experience of others as well as that of the present authors is that if the nidus is not totally excised, symptoms, most likely, will recur. Morrison, Hawes and Sacco[8] reported one case of their own, and added six from the literature, of recurrence of symptoms following incomplete excision of the tumor.

Since the diagnosis is uncertain short of microscopic examination, what the course of the disease might be if surgical intervention were not employed in cases of osteoid osteoma is unknown. Sherman,[1] in 1947, reported a case that clinically seemed to be osteoid osteoma and in which, over a period of 24 years, symptoms disappeared and the lesion in the bone became sclerosed. However, the steady progression of symptoms in most cases, and the excellent, immediate relief afforded by excision of the tumor, suggest that surgical measures constitute the best treatment for osteoid osteoma.

Summary

Osteoid osteoma is a small, benign tumor usually of endochondral bone, affecting mainly the long bones of the extremities and occurring not uncommonly among children. It produces pain which may disturb sleep and interfere with normal activities. The roentgenogram reveals a radiolucent area surrounded by osteosclerosis. This is suggestive of osteoid osteoma but differential diagnosis from certain other neoplastic, inflammatory and metabolic lesions of bone must be made. Thirteen children with osteoid osteoma have been treated by excision of the lesion at the Mayo Clinic. The results have been uniform alleviation of symptoms. This experience and that obtained elsewhere has shown that incomplete removal of the nidus may lead to recurrence of the symptoms.

Addendum

Since this paper was submitted, at the Mayo Clinic four additional lesions of children, aged 18 months to 10 years, have been proved by histologic examination of bone removed at surgical operation to be osteoid osteomas. One of the four children concerned, aged three years, is of particular interest since he was one of the 13 patients included in the foregoing report. He returned 10 months after the first operation complaining of pain in the same region as before. At the second operation, the osteoid osteoma was found almost in the same portion of the same bone, the lower part of the right tibia, but it seemed to be located more anteriorly than the lesion found previously. Because of this difference in location and the apparent complete removal of the nidus at the first operation, this lesion may represent a second osteoid osteoma rather than a recurrence.

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SPANISH ABSTRACT

Osteoma Osteoide en la Infancia

El osteoma osteoide es un pequeño tumor óseo de naturaleza benigna que crece generalmente dentro de cartílago y afecta principalmente los huesos largos de las extremidades y se presenta no raramente en niños. Produce dolor que puede perturbar el sueño e interferir con las actividades normales. La radiografía revela una zona transparente a los rayos X rodeada por esclerosis ósea. Aunque este caracter es sugestivo del osteoma osteoide, debe hacerse el diagnóstico diferencial con ciertas lesiones neoplásicas, inflamatorias y metabólicas de los huesos.

En la "Clínica Mayo" han sido tratados trece niños, con osteoma osteoide por excisión de la lesión lográndose el alivio de los síntomas. Nuestra experiencia y la obtenida en otras partes ha demostrado que la extirpación incompleta del foco tumoral puede determinar la recidiva de los síntomas.

Mayo Clinic

CHEMICAL COMPARISON OF NORMAL MECONIUM AND MECONIUM FROM A PATIENT WITH MECONIUM ILEUS

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MECONIUM,[1] the characteristic first stool of the newborn infant, has been shown recently to consist largely of a mucopolysaccharide which demonstrated a very high amount of blood-group-specific activity.[2-4]

In the pathologic condition known as "meconium ileus,"[5] the quantity of meconium is increased and the consistency of the substance is more viscid and mucilaginous than usual. This disorder is thought to represent the earliest and most severe form of cystic fibrosis of the pancreas, a disease characterized by diminution or absence of pancreatic enzymes.

In view of the lack of studies on meconium by modern chemical methods, a comparison of the meconium from a case of meconium ileus with that of normal infants appeared of interest.

EXPERIMENTAL

Materials Used: A pool of meconium specimens from 3 apparently healthy, normal babies and a specimen of meconium from a patient with meconium ileus were used for this study.

Chemical Analyses: All the determinations were done in duplicate. The dry weight was calculated by bringing the sample to constant weight at 100°C.; ash, by dry ashing in a platinum crucible; the total sugar and nitrogen as described previously;[4] material soluble in alcohol-ether, by a modification of the method in Hawk, Oser and Summerson;[6] and total phosphorus, by the method of Fiske and Subbarow.[7] NPN and acid-soluble phosphorus were estimated on the trichloracetic acid filtrate. The purines were determined according to the method of Hitchings[8] with the use of a double precipitation.

RESULTS

The results of the analyses on the meconiums are shown in table 1.

Normal meconium was found to contain more water and less ash than is present in normal feces. Nitrogen, purine and phosphorus were low and were largely water- and trichloracetic-acid-soluble. The amount of lipid material was relatively small. The most prominent component appeared to be a polysaccharide, which yielded a reducing sugar after acid hydrolysis. These data are therefore incompatible with the prevailing ideas about the composition of meconium as a chance collection of debris; they indicate the presence of a specific component, carbohydrate in nature as a consistent major constituent.

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Data for this paper are taken from a dissertation submitted to the Faculty of the Graduate School of the University of Cincinnati by Dorothy Jean Buchanan, June 1951, in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

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Other studies[3,4] indicated that the sugar consisted of galactose, hexosamine and methylpentose. Glucose and glycogen were absent.

Meconium from a patient with meconium ileus differed greatly from normal meconium. The percentage of carbohydrate was comparatively low. It contained larger amounts of nitrogen, most of which was precipitated by trichloracetic acid, as were most of the phosphorus and purine. It also had a component which could be coagulated by heat, and precipitated by ammonium sulfate, tannic acid, and sulfosalicylic acid.

Dialysis: About 13% of the reducing sugar content in normal meconium was dialyzable. When dialysis of the nondialyzable portion was repeated, only a minimal amount of reducing sugar diffused. This indicated that the dialyzable portion represented a definite fraction. The reducing sugar to nitrogen ratio was higher after dialysis, possibly

TABLE 1

ANALYSIS OF NORMAL MECONIUM AND MECONIUM FROM PATIENT WITH MECONIUM ILEUS

Meconium	Dry wt.	On Dry Weight Basis					NPN	Purine N	Free Reducing Sugar	Acid-Soluble P
		Ash	N	Ether-Alcohol Extractable	Total Reducing Sugar	Total P				
	%	%	%	%	%	%	% of total N	% of total N	% of total R.S.	% of total P
Normal	27.6	4.0	6.9	12.3	35.5	0.04	84.1	1.4	3.1	57
Ileus	29.8	1.8	14.4	9.7	8.7	0.07	5.4	2.9	2.7	9

indicating the removal of amino acids and small protein fragments which were not essention components of the material composing the greater part of meconium.

Nineteen per cent of the reducing sugar content of the dialyzable portion was free. The dialyzable portion was soluble in alcohol and in a phenol-alcohol mixture. This fraction also possessed no blood group activity, as compared to the high activity of the original material, thus confirming the above theory that this fraction consisted largely of fragments and breakdown products of the main components of meconium.

In meconium from a patient with meconium ileus about 15% of the reducing sugar was dialyzable, and upon repeat dialysis of the nondialyzable portion, no further diffusion of reducing sugar occurred. It was thus shown that, as in normal meconium, the nondialyzable portion represented a definite fraction.

Ammonium Sulfate Fractionation: When a normal meconium suspension, after removing the water-insoluble material by centrifugation, was treated with saturated ammonium sulfate at 4°C., no significant precipitation occurred until a saturation of 83% was reached. Complete saturation with ammonium sulfate resulted in the formation of a further precipitate. Determination of the reducing sugar in each fraction after dialysis showed that approximately the same amount of material was present in each precipitate and that some material remained in solution even after saturation with ammonium sulfate.

When a sample of meconium from a patient with meconium ileus was treated similarly, after removing the water-insoluble material by centrifugation, the first definite precipitate separated at a saturation of 67% ammonium sulfate. This precipitate was quite bulky and had a reducing sugar to nitrogen ratio of 0.44, which rose to 0.51 on reprecipitation, as compared with a ratio of 0.60 in the original suspension. Another less abundant precipitate separated at 75% saturation and had a reducing sugar to nitrogen ratio of

TABLE 2

ALCOHOL FRACTIONATION OF MECONIUM

Sample	Reducing Sugar	N	Ratio R.S./N.
	mg.	mg.	
Normal Meconium			
I. 46% alcohol	73.8	23.0	3.2
II. 50% alcohol	24.0	8.2	2.9
III. 60% alcohol	128.8	26.8	4.8
IV. 67% alcohol	168.8	34.2	4.9
V. 75% alcohol	392.5	73.5	5.3
VI. 83% alcohol	63.1	9.6	6.6
Meconium Ileus			
I. 56% alcohol	3.0	6.4	0.47
II. 62% alcohol	3.1	5.2	0.60
III. 66.5% alcohol	1.9	2.6	0.73
IV. 81% alcohol	0.7	2.6	0.27
V. Supernatant	0.6	0.7	0.86

0.10, which rose to 0.15 on reprecipitation. These results thus indicated two distinct fractions in the abnormal meconium. The supernatant contained some nitrogen but no reducing sugar. Although its composition was not investigated, it may be assumed to contain amino acids or polypeptides.

Alcohol Fractionation: The alcohol fractionation of normal meconium was found to be dependent upon the pH and the amount of buffer employed. The most reproducible results were obtained with a 0.2 M acetate buffer at pH 5.65 at 4°C. The results (reported in more detail in Buchanan[4]) after two repeated fractionations are shown in table 2.

In no fraction was the carbohydrate portion separated from the nitrogen, and after repeated fractionation, the carbohydrate to nitrogen ratios rose as the alcohol concentration rose. All the fractions possessed blood group activity, thus indicating that normal meconium consisted of several mucopolysaccharides in which the reducing sugar and the nitrogen components could not be separated.

A sample of meconium from a patient with meconium ileus, after removal of the water-insoluble material, was fractionated under the same conditions as the normal meconium by carefully adding 95% alcohol at 4°C., yielding the fractions shown in table 2. These results, as for normal meconium, indicated that the meconium from a patient with meconium ileus contains several mucoproteins, each of which possessed a characteristic reducing sugar to nitrogen ratio.

Action of Pepsin and Trypsin on Normal Meconium and Meconium from a Patient with Meconium Ileus: Peptic Digestion.—Samples of the meconium suspension in 0.01 N hydrochloric acid and preserved with toluene were treated with about 200 μg. of crystalline pepsin and allowed to incubate at 38°C. After 48 hours and again after another 72 hours, another 200 μg. of the enzyme were added.

Tryptic Digestion.—Samples of the meconium suspension in 0.1 M phosphate buffer, pH 7.6, and preserved with toluene, were treated with about 200 μg. of crystalline trypsin and allowed to incubate at 38°C. After 48 hours and again after another 72 hours, another 200 μg. of the enzyme were added.

TABLE 3

ACTION OF PEPSIN AND TRYPSIN ON NORMAL MECONIUM AND MECONIUM FROM PATIENT WITH MECONIUM ILEUS

Sample	Total N	NPN	% of Total
	mg.	mg.	
Ileus			
Original	4.28	0.27	6.3
Peptic digest	—	2.75	64.2
Tryptic digest	—	0.53	12.4
Normal*			
Original	2.43	1.30	53.5
Peptic digest	—	1.53	63.0
Tryptic digest	—	1.72	70.8

Sample	N	% of Total	Reducing Sugar	% of Total
	mg.		mg.	
Ileus				
Original	4.28	—	2.79	—
Peptic dialyzable	2.11	49.4	0.36	12.9
Peptic nondialyzable	1.78	41.6	2.14	76.6
Tryptic dialyzable	0.43	10.1	0	—
Tryptic nondialyzable	3.36	78.5	2.25	80.7
Normal				
Original	2.43	—	10.89	—
Peptic dialyzable	0.79	32.7	1.53	14.1
Peptic nondialyzable	1.65	67.8	7.49	68.8
Tryptic dialyzable	0.66	27.0	1.46	13.4
Tryptic nondialyzable	1.78	73.3	7.71	70.8

* This was a different pool of meconium specimens than that used on p. 304 which had a lower proportion of NPN.

Characterization: Samples of each of the digestions were analyzed for total and nonprotein nitrogen.

Another 2.0 cc. sample of each digestion was dialyzed against 20 cc. of distilled water for 21 hours. Aliquots of each of the dialyzable and nondialyzable portions were tested for their reducing sugar and nitrogen contents.

The results of these determinations are shown in table 3.

DISCUSSION

Normal meconium was found to consist largely of a carbohydrate component which yielded reducing sugars, most of which were nonfermentable, upon hydrolysis. Dialysis of normal meconium revealed that the majority of the carbohydrate was not diffusible. Fractionation with ammonium sulfate and alcohol indicated that normal meconium contained several similar but distinct fractions, in which the carbohydrate residue appeared to be firmly attached to a nitrogen residue which was nonprotein in reaction. The carbohydrate to nitrogen ratio appeared to be characteristic for each fraction.

These reactions and the demonstration that these materials possessed blood-group-specific activity indicate that the main components of normal meconium are mucopolysaccharides.

Not only were the physical appearances of normal meconium and that from a patient with meconium ileus different, but also their chemical composition.

Meconium from a patient with meconium ileus contained less carbohydrate and more nitrogen which behaved like a protein in its precipitation reactions—that is, it contained heat-coaguable material and yielded precipitates with trichloracetic acid, tannic acid and sulfosalicylic acid. It also gave indications that it contained several distinct fractions when a suspension of meconium ileus was treated with alcohol or ammonium sulfate. Each fraction possessed a characteristic carbohydrate to nitrogen ratio. These fractions may be considered as relatively stable, characteristic complexes of mucopolysaccharides with protein, since they required drastic measures for splitting.

Both forms of meconium were found to contain very little purine and phosphorus, thus indicating that the theory that meconium formed as a result of the accumulation of

TABLE 4

MECONIUM FROM PREMATURE INFANT

Section of Intestine	cm.	Ratio R.S./N.
I. Rectum		6.08
II. Sigmoid colon	2.5	5.12
III. Sigmoid colon	2.5	6.16
IV. Descending colon	5.1	5.59
V. Descending colon	5.1	3.92
VI. Transverse colon	5.1	4.43
VII. Transverse and ascending colon Appendix	12.7	2.53
VIII. Ileum	12.7	1.48
IX. Ileum	20.3	1.57
X. Jejunum	22.8	1.14
XI. Jejunum	22.8	1.10
XII. Duodenum	45.7	0.75

the cellular residues and nuclei of desquamated cells from the gastrointestinal tract during fetal development was no longer tenable.

Pepsin was found to have considerable digestive power on meconium from a patient with meconium ileus under the conditions employed, but little action on normal meconium. Under the conditions used, trypsin showed very little activity on either normal meconium or that from a patient with meconium ileus.

Proteolytic enzymes, presumably of pancreatic origin for the most part, normally digest the protein portion of the meconium, leaving the mucopolysaccharides practically intact. The persistence of protein in the meconium of the infant with meconium ileus, is probably accounted for by the lack of tryptic enzyme production in the pancreas or failure of its secretion into the intestine. The abnormally high viscosity of the abnormal meconium may be attributed to the fact that frequently mucoproteins exhibit higher viscosities than mucopolysaccharides.

In order to obtain evidence for a digestive process *in vivo,* it was of interest to study the changes in meconium during its passage through the intestine. The intestinal tract of a premature infant, born after approximately seven months' gestation, was divided into sections and the meconium expressed. The reducing sugar to nitrogen ratios indicate a changing composition of meconium in the direction of decreasing protein content during

its progress in the intestinal tract, probably owing to the action of proteolytic enzymes. (See table 4.)

These results suggest that meconium is formed from a secretion of the body which is high in protein and in blood-group activity. Gastric juice may be one of the principal sources. The persistence of protein in the meconium of infants with meconium ileus is in keeping with the analyses of the contents of different portions of the intestine of a premature infant, which indicated that the contents of the duodenum had the highest protein admixture. However, other secretions must contribute to the formation of meconium, as indicated by the presence of meconium in infants with high and mid-gut atresia portions of the intestine distal to the point of obstruction.

Summary

A series of chemical analyses comparing normal meconium with meconium from a patient with meconium ileus demonstrated the following differences:

a. Normal meconium contained over four times the amount of total reducing sugar found in the meconium from a patient with meconium ileus. About 15% of the reducing sugar of both the normal and the abnormal meconium was dialyzable.

b. Normal meconium contained less total nitrogen than meconium from a patient with meconium ileus. Most of this was found to be nonprotein, while that of the abnormal meconium was mostly protein in nature.

c. The phosphorus and purine contents were minimal in both samples.

The ammonium sulfate fractionation of normal meconium differed from that of meconium from a patient with meconium ileus.

Alcohol fractionation of normal meconium gave precipitates whose reducing sugar to nitrogen ratios rose from 3.2 to 6.6 with increasing alcohol concentrations. Meconium from a patient with meconium ileus gave precipitates whose reducing sugar to nitrogen ratios rose from 0.47 to 0.86 with increasing alcohol concentrations.

The action of pepsin and trypsin on normal meconium was not significant; on meconium from a patient with meconium ileus trypsin increased the per cent of nonprotein nitrogen twice and pepsin, six-fold.

The reducing sugar to nitrogen ratio of meconium from a premature infant was shown to increase as it proceeded down the intestinal tract.

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SPANISH ABSTRACT

Comparación Química Entre el Meconio Normal y el Meconio Obtenido de un Paciente con Meconium Ileus

En una serie de analisis quimicos comparativos entre el meconio normal y el meconio de un paciente con meconium ileus se demostraron las siguientes diferencias: el contenido de azúcares reductores en el meconio normal es cuatro veces más alto que en el meconio perteneciente al paciente con meconium ileus; el meconio normal contiene menos nitrogeno total, nonproteinico en su mayor parte, que el contenido en el meconium ileus, en el cual el nitrogeno es de naturaleza proteinica en su mayor parte; el contenido de fosforo y purinas fueron mínimos en ambas muestras de meconio.

Aproximadamente un 15% de los azúcares reductores de ambos meconios fueron dializables. El fraccionamiento con sulfato de amonia resultó en la producción de precipitados definitivos a una saturación de 85% y a saturación completa. Fraccionamiento con alcohol del meconio normal produjo precipitados a concentraciones de alcohol de 46, 60, 67, 75, y 83%, con elevación del "ratio" azúcares reductores-nitrogeno de 3.2 a 6.6 con el aumento de las concentraciones de alcohol. Fraccionamiento con alcohol del meconio ileus produjo precipitados a concentraciones de alcohol de 56, 62, 66.5 y 81%, con una elevación de el "ratio" azucares reductores-nitrogeno de 0.47 a 0.86 con el aumento de las concentraciones de alcohol.

La actividad de la pepsina y tripsina del meconio normal no fué significativa, pero estuvo aumentada en el meconio del paciente con el meconium ileus.

Sé observó que el "ratio" azucares reductores-nitrogeno del meconio obtenido de un niño prematuro aumentada con la progresión intestinal del meconio.

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GASTROINTESTINAL ALLERGY IN INFANCY

Significance of Eosinophiles in the Stools

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THE purpose of this paper is to report on a series of 60 infants having gastrointestinal disturbances which appeared to be on an allergic basis, and to correlate the clinical evidences of allergy with the demonstration of rectal eosinophilia.

Allergic bases for certain common gastrointestinal disorders in infants have been referred to repeatedly. Cohen and Breitbart[1] presented evidence that both pylorospasm and pyloric stenosis were diseases of allergy. Of 27 cases, they found a significant proportion that exhibited a positive family history of allergy, positive skin tests by both direct and passive transfer methods, and other allergic manifestations. These included eczema, urticaria, angioneurotic edema, asthma, hay fever, vasomotor rhinitis and drug eruptions. They reported that one or more of these conditions occurred in 44% of their cases prior to the age of 12.

Balyeat and Pounders[2] reported a severe case of pylorospasm that showed loose mucoid stools, colic, positive family history of allergy, and later developed eczema. This case was operated twice for an erroneous diagnosis of pyloric stenosis before the allergic nature of the condition was recognized. This infant was later demonstrated to be allergic to cow's milk and egg. McCarthy and Wiseman[3] reported six cases of pylorospasm with vomiting, diarrhea, colic and fretfulness, all of whom later developed eczema, all apparently due to milk allergy. One developed anaphylactic shock.

Kunstadter[4] reported three cases of the celiac syndrome, clearing up completely with elimination of cow's milk. Campbell[5] and Clein[6] observed that the first symptoms of allergy appeared in early infancy in a high percentage of their cases. Schwarz,[7] studying the pediatric records of allergic adults, noted the high incidence of frequent loose, foamy, frothy stools, pylorospasm, colic, pyloric stenosis and in older children abdominal pain and cyclic vomiting. Lapin and Weissberg[8] reported a series of patients with allergic diarrhea, some of whose symptoms simulated those of the celiac syndrome. Characteristic proctoscopic findings were reported. These investigators with Fried[9] later exhibited cases of allergic pylorospasm and colitis at a meeting of the American Academy of Pediatrics. Almost all these investigators have called attention to the importance of allergy to cow's milk.

Nance[10] demonstrated the presence of numerous eosinophiles in the stools of infants having certain types of diarrhea, colic or vomiting, and presented clinical evidence that these symptoms were on an allergic basis. He proposed this procedure as a rapid aid in detecting gastrointestinal allergy. In another report[11] he described the cytology of the stools in a variety of nonallergic conditions, in which eosinophiles were invariably absent. Urbach and Gottlieb[12] also stated that the outstanding characteristic of allergic

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intestinal disease is the high eosinophile content in the stools. Gay[13] and Andresen[14] also reported the significance of stool eosinophiles in allergic intestinal conditions. Ingelfinger, Lowell and Franklin,[15] in a comprehensive review of gastrointestinal allergy, point out the skepticism and conflicting views on the subject. They state that while the diagnosis is frequently entertained, it is rarely established. They point out the extreme difficulties in proving a diagnosis of gastrointestinal allergy, even with all known laboratory procedures. They indicate the need for establishing a characteristic clinical and laboratory pattern in a group of proved cases.

This study covers a period of 16 months during which cytology of stool smears has been correlated with clinical symptomatology in all the cases of suspected gastrointestinal allergy, with nonallergic gastrointestinal conditions, and also a large group of normal infants and children. A decided stool eosinophilia was demonstrated in 60 patients, the symptomatology and clinical course of which are to be presented. In 76 cases, stool smears were negative for eosinophiles. These included cases of bacillary dysentery, cystic fibrosis of the pancreas, amebic dysentery, diarrheas of undetermined cause, and normal infants having normal stools. There was nothing in the clinical course of these 76 cases to indicate any evidence of active allergy during the period of observation.

A satisfactory technic is essential in demonstrating stool eosinophiles. They are generally found in the mucoid portion of the stool. Hence an effort should be made to separate the mucus from the fecal matter. The specimen should be fresh. A specimen obtained by insertion of the finger is very satisfactory. The smear is allowed to dry without heat, so as not to affect the staining qualities and morphology of cells. The May-Grünwald stain has been found to be satisfactory for demonstrating eosinophiles in the stool as well as in nasal smears. The undiluted stain is applied for 30 seconds. It is then diluted with an equal quantity of distilled water, and allowed to stand an additional 30 seconds before final washing. This gives a satisfactory stain in the majority of cases, although occasionally the stain may be too light, in which case it is restained by the same technic. Stool smears vary markedly in staining qualities. Eosinophiles generally appear bright red, and granules are clearly visible. Occasionally they appear pale pink, or dark reddish brown. The shape of the cell is often distorted, and disintegrated eosinophiles are often seen, with granules spread out.

Stool smears were studied for their content and distribution of eosinophiles, and for the presence of other types of cells. They were also examined for pathogenic bacteria and parasites. The smears could be classified into four major groups according to their eosinophile content as indicated in table 1. Group 1 showed numerous eosinophiles, arranged in clumps, resembling the appearance of a nasal smear in an active hay fever. Group 2 showed numerous scattered eosinophiles but few or no clumps. Group 3 showed occasional eosinophiles in scattered fields. Group 4 showed no eosinophiles. The 60 cases that com-

TABLE 1

CLASSIFICATION OF STOOL SMEAR BY EOSINOPHILE CONTENT

Group	Cytology of Smear
1	Large clumps of eosinophiles
2	Numerous scattered eosinophiles
3	Occasional eosinophile
4	No eosinophiles

TABLE 2

INCIDENCE OF SYMPTOMS

Symptom	No. Cases	%
Diarrhea alone	19	31.6
Vomiting alone	5	8.3
Colic alone	3	5.0
Diarrhea and vomiting	9	15.0
Diarrhea and colic	10	16.0
Diarrhea, colic and vomiting	12	20.0
Total diarrhea	50	83.3
Total vomiting	28	46.6
Total colic	27	45.0
Total infants	60	100.0

prise the present study are in Groups 1 and 2. Their stool smears showed large numbers of eosinophiles either in clumps or scattered throughout the slide. The 76 cases showing no evidence of allergy are in Groups 3 and 4. Patients having infectious diarrhea often showed large numbers of mononuclear or pus cells in their stool smears, but eosinophiles were absent or rare.

Analysis of symptomatology in the 60 cases with positive stool smears is shown in table 2. It is noted that the symptoms are diarrhea, vomiting or colic, either alone or more often in various combinations. Diarrhea is the most common symptom, being almost twice as common as vomiting or colic. It has been noted that the marked stool eosinophilia in these infants is present only when symptoms are active, and subsides when symptoms disappear. However, in such infants, some eosinophilia can almost always be demonstrated.

The outstanding macroscopic feature of the stools in these allergic diarrheas is the abundant mucus. They are generally loose and frequent, and may be profuse and watery. They do not have the foul purulent appearance often seen in infectious diarrheas. In some cases there is an excess of extracellular undigested fat and starch, as demonstrated by stool emulsions stained with Sudan IV and Lugol's iodine. These cases simulate the celiac syndrome, and when accompanied by allergic bronchitis, may bear a close resemblance to fibrocystic disease of the pancreas. Four such cases were observed, with normal amounts of trypsin in the stools as determined by the gelatin film method. The marked stool eosinophilia, and the response to specific elemination therapy is further presumptive evidence of the allergic nature of such diarrheas. The general physical condition of these infants remained remarkably good. Three cases, however, were severe enough to require hospitalization and the administration of parenteral flujds. While the age of onset was predominately in the early months, 35% began after the third month, and a few after the first year.

In a large number of these children (table 3) there were other associated signs of allergy, and a positive family history. Spontaneous remissions and exacerbations occurred in some cases. Most of these patients were resistant to ordinary types of therapy for diarrhea, but responded promptly when offending foods were removed. Cow's milk was the most common offender.

During recovery, stools became normal and pasty in appearance; eosinophiles were reduced or absent. Repeated cultures and smears of these diarrheal stools did not reveal any pathogens.

TABLE 3

INCIDENCE OF OTHER MANIFESTATIONS OF ALLERGY

Manifestation	No. Cases	%
Positive family history*	36	83.7
Eczema only	13	21.6
Eczema and asthma	5	8.3
Eczema and croup	1	1.6
Asthma only	4	6.6
Asthma and eczema	5	8.3
Asthma and croup	1	1.6
Croup only	3	5.0
Total eczema	19	31.6
Total asthma	10	16.6
Total croup	5	8.3
Total infants	60	100.0

* Family follow-up was available on 43 cases.

The onset of vomiting occurred early in infancy, generally in the newborn period. In spite of protracted vomiting, these infants generally gained weight and remained in good physical condition. The type of vomiting varied from a slight regurgitation to projectile emesis. Pyloric waves were often present, even in the absence of pyloric stenosis. Other stigmata of allergy were often present. These included eczema, asthma, rhinitis and croup. A positive family history was frequently present. The stools of these babies contained abundant mucus, even though they were not necessarily diarrheal.

Seven cases of pyloric stenosis that showed a stool eosinophilia prior to surgery are included in this series. Six of these had positive family histories of allergy. One had bouts of eczema, asthma and diarrhea. Both parents of this infant had hay fever and asthma. One sibling was asthmatic, and another had hives. This infant required surgical intervention twice, having had a recurrence of the pyloric obstruction 72 days after the first operation. At surgery the site of the previous operation on the pylorus could not be identified.[16] Four other cases of pyloric stenosis that did not show a stool eosinophilia are being followed. If allergy is present in these infants, it has not yet become obvious. All these cases of pyloric stenosis were subjected to surgery, and all made good recoveries. It was not possible to obtain a satisfactory result with conservative medical management, which included elimination diets, phenobarbital and atropine, and general supportive therapy. All were operated soon after the diagnosis was confirmed, and medical management appeared futile.

Colic likewise had its onset early in life in the majority of cases. These babies were fretful and unhappy. Some had severe cramps. Their physical condition remained good. The colic was resistant to ordinary formula changes, but generally responded to the removal of the allergenic foods. Again the commonest offender was cow's milk. Stools contained an abundance of mucus, and other evidences of allergy were often present in these babies, as well as in their families. While the highest incidence of colic was in the first three months, it did not always follow the pattern of so-called "three month" colic. Five cases began after the end of the third month, and one at the end of a year.

A high incidence of other allergic manifestations in these infants is indicated in table 3. Eczema had occurred in 32% of these infants at the time this study was compiled. Only

six cases were severe and generalized, while the others varied from mild to moderate involvement. All these were believed to be atopic eczema. The eczema was generally preceded by gastrointestinal symptoms, although in a few cases they were simultaneous. Asthma occurred in 17% of these babies. Attacks of wheezing were often precipitated by upper respiratory infections. Asthma in some cases appeared to be related to food allergy. Paroxysmal cough, possibly due to allergic bronchitis, was so marked and distressing in some cases that the possibility of pertussis had to be entertained. Attacks of croup occurred in 8.5% of these babies. These were generally related to upper respiratory infections, and were of the spasmodic type. They often responded to adrenalin in the same way as asthma. It has been the authors' impression that spasmodic croup frequently occurs in patients with allergic backgrounds. The present observations give evidence of this. It has also been observed that many of these babies have attacks of rhinitis with profuse nasal discharge. The discharge has on repeated occasions been demonstrated to contain large numbers of eosinophiles.

These infants were treated by the removal of the offending foods from the diet. This problem was relatively simple because of the young age group involved. Many of these infants had numerous formula changes prior to the time they came under the authors' observation. However, such changes generally involved various modifications of cow's milk. It has been observed in this study, and also in others, that cow's milk is the most common offender in early infantile allergies. Hence it is not surprising that formula changes from one type of cow's milk to another is not constantly productive of results.

Types of therapy that were followed by alleviation of symptoms are indicated in table 4. Mild cases often responded to evaporated cow's milk. Terminal sterilization was used, thus subjecting the milk to additional heat. This type of formula is less antigenic than fresh cow's milk, as the proteins have been denatured by heat and pressure, and there is also the advantage of economy. Goat's milk was used in cases that did not respond to any form of cow's milk. Canned goat's milk was generally used because of its convenience. It also has the advantage of being denatured by heat and pressure. It was generally readily accepted by both infant and mother, and gave satisfactory results in a number of cases that did poorly on evaporated cow's milk.

TABLE 4

TYPES OF DIETARY THERAPY FOLLOWED BY REMISSION

Type of Feeding	No. Cases
Evaporated goat's milk	16
Evaporated goat's milk boiled 6 hr.	1
Fresh boiled goat's milk	1
Evaporated cow's milk	16
Evaporated cow's milk boiled 6 hr.	1
Enzylac milk ®	1
Nutramigen ®	5
Mull-soy ®	3
Breast (mother on elimination diet)	2
Elimination of orange juice	3
Elimination of eggs	5
Spontaneous cures	6
Total no. observed	60

In cases that failed on both cow's milk and goat's milk, other milk substitutes were used. There was no logical way to determine ahead of time which formula was to be successful. Nutramigen® was successful in several cases that were resistant to both cow's milk and goat's milk. Mull-soy® gave satisfactory results in a few cases that were unimproved by goat's milk or nutramigen®.

It was observed that when substituting one formula for another, at least one week's trial was necessary before drawing conclusions. Frequent changes confuse the situation. However, if the infant seemed decidedly worse after a new formula, the trial period would be cut short. It was also observed that when the offending food was removed from the diet, the infant could tolerate an otherwise full unrestricted diet.

It was also observed that symptoms would return after reintroduction of offending foods. One infant had marked diarrhea, vomiting and a shocklike state following the ingestion of egg. A stool smear taken at this time showed an eosinophilic infiltration equivalent to that of a nasal smear in active hay fever, as in Group 1. In spite of instructions regarding elimination of egg, this infant was again given egg by the mother after he was symptom-free, and the entire syndrome recurred. Another infant, a premature, had diarrhea for five weeks. This diarrhea would invariably abate when breast milk was used, but recur when any type of cow's milk was substituted. A smear for eosinophiles taken when the diarrhea was active showed a heavy infiltration with large clumps. The diarrhea subsided promptly when nutramigen® was substituted as a food, and did not recur. Similar observations appear in Cases 1, 2 and 3.

After these infants were adjusted to a satisfactory formula, new foods were cautiously added, one at a time. Wheat and eggs were common offenders, and were excluded from the diet. Barley cereal was generally accepted without symptoms, although one infant could not tolerate any type of cereal up to the age of one year. Meat rarely caused trouble. After 6 to 9 months of age, most of these infants could tolerate cows' milk. It was also generally possible to introduce wheat and sometimes eggs into the diet of these older infants. It was found in some instances where the infant could not tolerate either evaporated cow's milk or goat's milk, boiling the milk in the can for 4 to 6 hours made it acceptable. Synthetic vitamins were used exclusively.

Blood counts have not been helpful and have not been done routinely. The blood eosinophile count, while occasionally elevated, has not correlated regularly with the presence of active allergy. The same situation is known to prevail in hay fever, where the blood eosinophile count is often normal, despite marked local eosinophilia. Skin tests have been performed in some of these babies. Although a few positive ones have been found, they generally furnished no useful information. In many cases of proved sensitivity to milk, skin tests were negative. In three cases, however, positive skin tests were obtained to milk and eggs, which correlated with the clinical observations of intolerance to these foods. These three patients had severe diarrhea, colic and vomiting, and were intractable to all therapy until cow's milk was removed from the diet. A better test for food allergy was found to be the reduction of stool eosinophilia and the disappearance of symptoms when the allergenic food was removed from the diet.

Case Histories

1. W. I., a white male, was first seen at 6 wk. of age, with a history of intractable diarrhea from birth, colic and vomiting. Numerous formula changes resulted in no improvement. A stool smear showed a high mucus content, with clumps of eosinophiles. A change to a goat's milk formula was

followed by almost complete relief of all gastrointestinal symptoms, with reduction of the stool eosinophilia. Episodes of asthma and eczema subsequently occurred. Fresh cow's milk was tolerated at the age of 18 mo. The infant's mother had had eczema most of her life.

2. K. M., a white female, had a history of intractable diarrhea, fretfulness and regurgitation from the age of 2 mo. She was first seen at the age of 3 mo. after numerous unsuccessful formula changes. Stools were high in mucus and eosinophile content. Stools also contained an excess of neutral fat, suggestive of the celiac syndrome. An older brother had a severe pollinosis with hay fever and asthma. A change to a goat's milk formula was not followed by any improvement. Complete relief of all symptoms was obtained after 1 wk. on a nutramigen® formula. Several relapses occurred when cow's milk was deliberately reintroduced into the diet, and at these times the eosinophile content of the stools again became high. She showed positive skin tests to milk and egg. After 1 yr., she was able to tolerate cow's milk, and had normal growth and development.

3. A. K., a white female, had a history of spitting, flatulence and fretfulness from birth. There was no diarrhea. A stool smear showed a high eosinophile content. A change of formula to goat's milk at the age of 6 wk. was followed by a marked improvement in all symptoms, and a disappearance of eosinophiles from the stools. Recurrence of symptoms occurred on 2 occasions when cow's milk was reintroduced. After 6 mo. of age, this baby tolerated cow's milk without symptoms, and did not develop any other allergic symptoms.

4. M. I., a white male, had onset of diarrhea at the age of 15 mo., which was resistant to numerous dietary changes, paregoric, kaopectate and bismuth. Stool cultures and smears for parasites were negative. A smear after 2 mo. of diarrhea showed a high eosinophile content, and an excess of extracellular starch. A change to a goat's milk formula produced no improvement. The child was then put on a milk-free diet, and the diarrhea cleared completely within 1 wk. He tolerated mull-soy® as a milk substitute with no recurrence of symptoms. This infant had several bouts of asthma, the first at the age of 11 mo., and had a mild eczema of the cheeks at 4 mo. A brother had eczema and asthma.

5. S. R., a white male, had onset of severe diarrhea at 2 wk. of age. Projectile emesis occurred at 4 wk., and marked pyloric waves were seen. Fretfulness was present from birth. A stool smear at 1 mo. revealed large clumps of eosinophiles. A change of formula to evaporated goat's milk resulted in relief of all symptoms. This baby had wheezing episodes with upper respiratory infections, and also several bouts of spasmodic croup. The father has a marked pollinosis with hay fever and asthma. The father has 2 brothers who also have hay fever and asthma.

These five case histories illustrate various aspects of allergic intestinal disease in infants. The other cases were equally clearcut.

In the course of this study, it was noted repeatedly that the symptoms seemed to date back to the newborn period, and numerous positive stool specimens were obtained in infants several weeks old. This observation prompted an examination of stools of newborn infants in the newborn nursery. Specimens have been examined on 65 babies from the first to the seventh day of life. Of these, 13 have shown a significant eosinophilia. The significance of these observations will have to be determined by follow-up studies.

Discussion

This group of 60 infants was characterized by a marked stool eosinophilia that occurred during the times that gastrointestinal disturbances were active. It has also been observed that these infants in a high proportion of cases came from allergic families, and exhibited other allergic manifestations in the course of their development. The gastrointestinal disturbances could frequently be alleviated by the omission of one or more specific foods from the diet, and reproduced by the reintroduction of such food.

It would appear that a stool eosinophilia is associated with active gastrointestinal disturbances in infants with allergic trends. It may be suspected that the gastrointestinal disturbances are specifically on an allergic basis, and that the presence of large numbers of eosinophiles in the stools may be used as a diagnostic sign.

Summary and Conclusions

The syndrome of gastrointestinal allergy as observed in 60 infants is a clinical entity characterized by diarrhea, colic or vomiting, alone or in varying combinations. Diarrhea is almost twice as common as colic or vomiting.

The syndrome may be suspected upon the demonstration of clumps of eosinophiles, or large numbers of scattered eosinophiles in the stools. The stools are generally high in mucus content, and the eosinophiles are most numerous in the mucus. A rapid, easy method for demonstrating eosinophiles in the stool mucus is described.

The allergic nature of the signs and symptoms is further suggested by:

a. The positive family background of allergy.
b. The development of other major allergic manifestations in the subsequent course of these patients.
c. The striking frequency with which symptoms disappear after the removal of the offending food from the diet. This may be anything in the diet, but is generally cow's milk. Results may not be apparent until a week has elapsed after specific food elimination.
d. Recurrence of symptoms may be demonstrated upon readministration of the offending substance.

The ultimate fate of these babies with regard to the development of later allergic disturbances will have to await long range follow-up studies. It is hoped that the control of these early allergic manifestations may minimize later allergic symptomatology.

Evidence is presented that the first allergic disturbances may occur in the newborn period.

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SPANISH ABSTRACT

Alergia Gastrointestinal en la Infancia; Significación de la Presencia de Eosinófilos en las Evacuaciones

Varias publicaciones acerca de trastornos gastrointestinales como el piloroespasmo, estenosis pilórica, síndromes celiacos, diarreas y colitis en niños cuya etiología parecía ser alérgica han aparecido desde hace algunos años. Se apoyaba esta afirmación en las manifestaciones alérgicas de los enfermos: historia familiar alérgica, cutireacciones positivas, eczema, urticaria, edema angioneurótico, asma, fiebre de heno, rinitis vasomotora y erupciones medicamentosas. Estos trastornos los presentaron simultáneamente con las manifestaciones gastrointestinales o en años posteriores. El alérgeno mas importante fué la leche de vaca y en algunos la exclusión de la misma curó el cuadro.

Por otra parte, estudiando los antecedentes gastrointestinales de la infancia de un grupo de enfermos alérgicos adultos, se hallaron trastornos como diarrea espumosa, piloroespasmo, cólicos, estenosis pilórica y en niños mas grandes, dolor abdominal y vómitos cíclicos.

Este estudio comprende un período de 16 meses de investigación de eosinófilos en las evacuaciones de 60 enfermos sospechosos de alergia gastrointestinal correlacionado con la sintomatología clínica que presentaban. En todos ellos se encontró eosinofilia franca. En otro grupo de 76 enfermos en que no había eosinofilia intestinal tampoco presentaron en su evolución clínica prueba alguna de alergia activa.

Diarrea, vómitos y cólicos fueron los síntomas que presentaron los enfermos alérgicos ya fuera aisladamente o en combinación. La diarrea fué dos veces mas frecuente que el vómito y cólico juntos. La eosinofilia intestinal aun fuera de los períodos activos pudo encontrarse fácilmente. La diarrea era de evacuaciones mucosas, blandas o líquidas, frecuentes o profusas. El cuadro se iniciaba aun desde los primeros meses de la vida.

El vómito se presentaba desde el período del recien nacido, en regurgitación o en proyectil, con o sin ondas pilóricas visibles. No obstante, la ganancia en peso era satisfactoria. Siete enfermos tenían estenosis pilórica con eosinofilia y antecedentes alérgicos familiares y personales. Las dietas de eliminación y antiespasmódicos fracasaron y solo la cirugía tuvo éxito.

El cólico, de los primeros 3 meses generalmente, a veces severo, no atacaba al estado general.

En el grupo total de casos había un 83.7% que tenían antecedentes alérgicos paternales y 57% tenian manifestaciones alergicas como eczema, asma y erupciones, aisladas o asociadas. El alérgeno mas importante fué la leche de vaca y su sustitución con leche de vaca evaporada o de cabra fue seguida de mas éxitos. El nutramigen era efectivo si aquellas fracasaban. Una semana de prueba fue necesario para apreciar resultados antes de administrar otra leche. Cuando se daba el alégeno causante el cuadro clínico reaparecía así como la eosinofilia intestinal.

La adición de nuevos alimentos a la formula lactea se hacía con precaución y uno solo a la vez, eliminando trigo y huevo. Generalmente después de los 6 ó 9 meses la mayor parte de los enfermos pudo tolerar la leche de vaca.

La eosinofilia sanguínea y cutireacciones con algérenos no prestaron ayuda diagnóstica.

En conclusión, el síndrome de alergia gastrointestinal debe sospecharse cuando se demuestra eosinofilia acentuada en las evacuaciones, historia familiar alérgica, coexistencia o aparición posterior de otros padecimientos alérgicos en el enfermo, la desaparición del cuadro clínico al suprimir el alérgeno y su reaparición al administrarlo nuevamente.

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SUSCEPTIBILITY OF HEMOPHILUS PARAPERTUSSIS TO CERTAIN ANTIBIOTICS

By ELIZABETH DAY, M.S., AND WILLIAM L. BRADFORD, M.D.
Rochester, N.Y.

SINCE 1937, when Hemophilus parapertussis was first described,[1,2] it has become a subject of interest because it causes an infection distinguishable from pertussis only by cultural methods. The incidence of the disease is not accurately known, but there is evidence that it is widely distributed. Between 1940 and 1950 73 strains of H. parapertussis have been isolated in Rochester in the course of routine examination of cultures taken for H. pertussis. The greatest number of strains have been isolated during the summer months; 21 during the summer of 1947. Of considerable interest is a recent report[3] that Lautrop, in Copenhagen, isolated 200 strains of the organism, representing about 20% of the total number of positive cultures examined for H. pertussis at the Serum Institute.

Although the antibiotic spectrum of H. pertussis is fairly well known, little information is available concerning that of H. parapertussis. This report concerns this subject because of the interest in the relationship of the two organisms and the probable increase in the frequency with which parapertussis infections may be encountered in the future.

MATERIALS AND METHODS

The present study concerns both *in vitro* and *in vivo* tests of the susceptibility of H. parapertussis to certain antibiotics and compares the results with those obtained with H. pertussis.

In vitro: Tests were made with 12 strains of the organism which had been lyophilized soon after isolation. The cultures were reconstituted and suspensions of the organism were standardized to a reading on the Klett-Summerson photo-electric colorimeter, so that the suspension contained approximately 10 billion organisms/cc. A standard loopful of the bacterial suspension was spread upon the surface of Bordet medium to which various 2-fold dilutions of the antibiotic had been added. After incubation at 37° C. for 72 hr. the degree of growth inhibition was observed. Results were recorded as the highest dilution resulting in no growth. All strains were tested simultaneously against a given antibiotic and the highest dilution of the drug giving complete inhibition of growth of 50% of the strains was calculated.[4]

In vivo: In these studies susceptibility was determined by observing the smallest amount of the antibiotic which protected 50% of a group of mice against death when injected intra-abdominally for 5 successive days. Standard white Swiss mice, weighing approximately 10 gm. each, were given a routine intranasal instillation of approximately 500 million organisms, while under light anesthesia. Ten mice were used for each subgroup receiving a particular dose of the drug. The first daily therapeutic injection was made 4 hr. after the intranasal inoculation. The number of mice surviving at the end of the 5 day period was observed and the dose of the antibiotic in mg./kg. body weight/day which protected 50% of the mice was calculated.

The antibiotic preparations tested were:

streptomycin (calcium chloride complex) (Merck)

crystalline penicillin G sodium (Merck) 1.666 units/mg.

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TABLE 1

H. PARAPERTUSSIS—IN VITRO SENSITIVITY OF 12 STRAINS

Antibiotic	Antibiotic μg./cc. Medium														μg./cc. Inhibiting 50% Cultures
	640	320	160	80	40	20	10	5	2.5	1.25	0.62	0.31	0.15	0.07	
Streptomycin	6*	5	0												421
Penicillin	12	12	4												266
Neomycin						12	12	0							7.0
Aureomycin							12	8	1	0					3.1
Chloramphenicol									12	0	0				1.7
Terramycin									12	8	0				0.74
Polymyxin B												12	11	5	0.13

* No. cultures completely inhibited.

neomycin sulfate (Commercial Solvents Corporation) (134 units/mg.)
aerosporin hydrochloride (polymyxin B) (Burroughs Wellcome & Company, Inc.)
chloramphenicol (chloromycetin) (Parke, Davis & Company)
terramycin hydrochloride (Pfizer)
aureomycin hydrochloride (Lederle)

DISCUSSION OF RESULTS

It is obvious (table 1) that the *in vitro* spectrum for the antibiotics tested against H. parapertussis covers a wide range; from 421 μg./cc. for streptomycin to 0.13 μg./cc. for polymyxin B. Listed in the order of their decreasing activity are polymyxin B, terra-

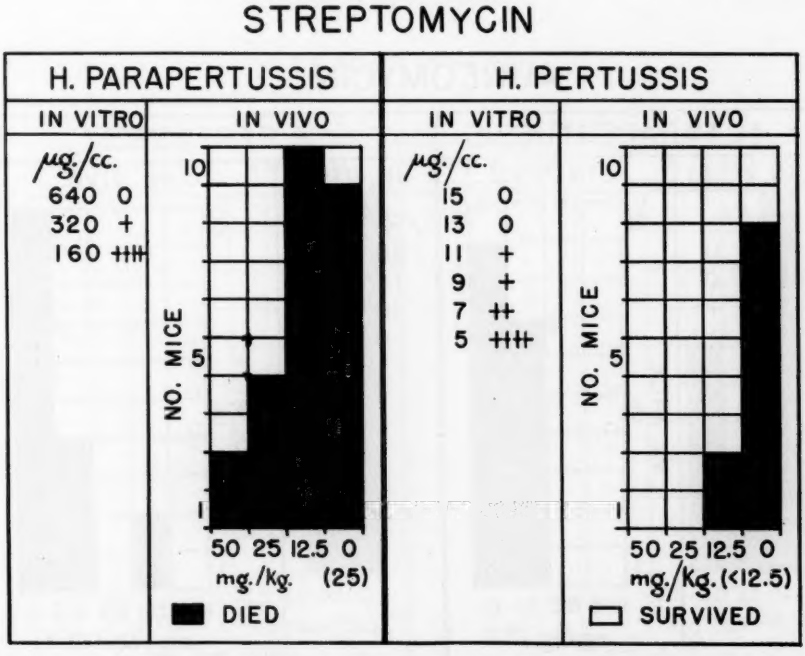

CHART A. Comparison of in vitro and in vivo action of streptomycin against H. parapertussis and H. pertussis.

NEOMYCIN

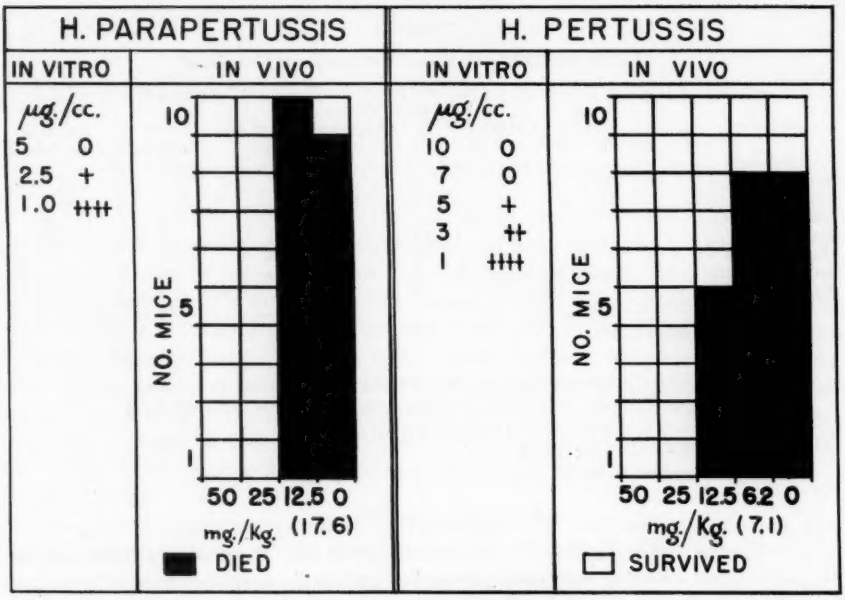

CHART B. Comparison of in vitro and in vivo action of neomycin against H. parapertussis and H. pertussis.

AUREOMYCIN

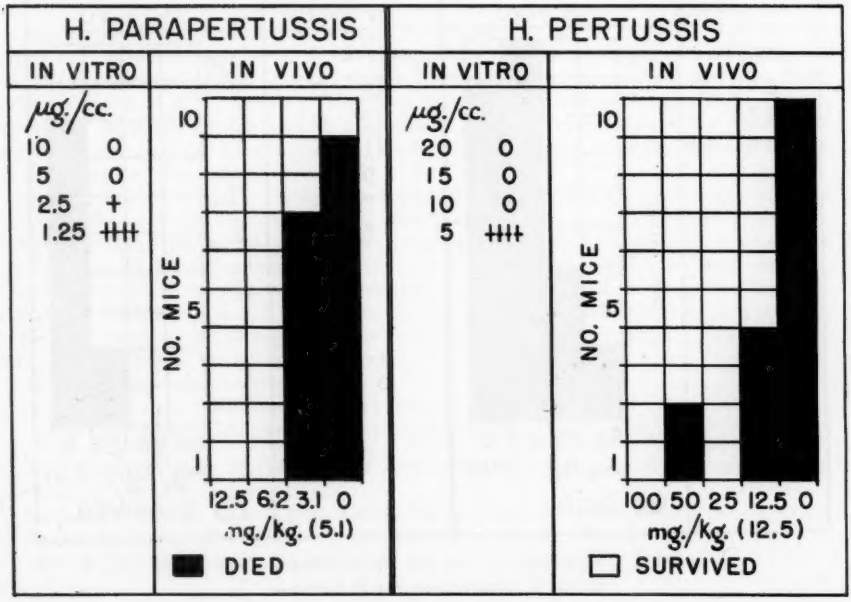

CHART C. Comparison of in vitro and in vivo action of aureomycin against H. parapertussis and H. pertussis.

CHLORAMPHENICOL

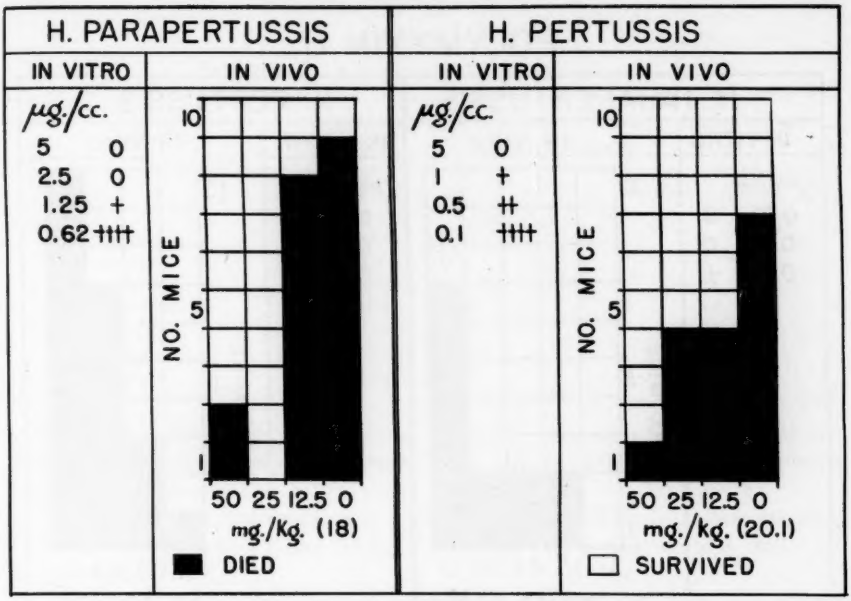

CHART D. Comparison of in vitro and in vivo action of chloramphenicol against H. parapertussis and H. pertussis.

TERRAMYCIN

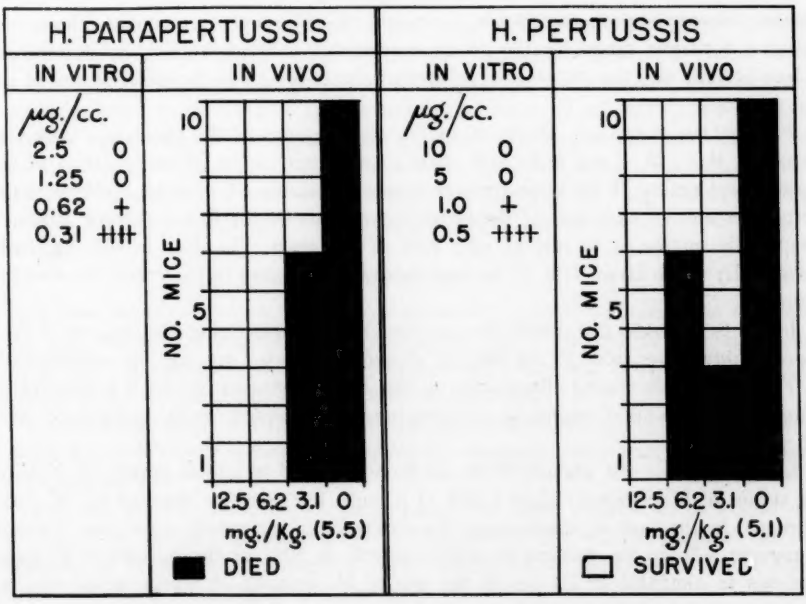

CHART E. Comparison of in vitro and in vivo action of terramycin against H. parapertussis and H. pertussis.

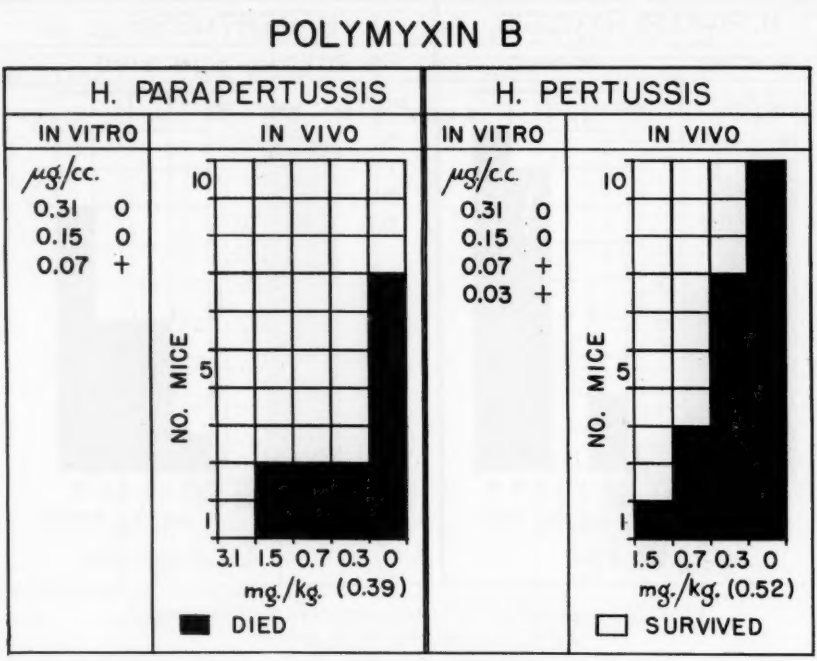

CHART F. Comparison of in vitro and in vivo action of polymyxin B against H. parapertussis and H. pertussis.

mycin, chloramphenicol, aureomycin, neomycin, penicillin and streptomycin. The results indicate a narrow range for the group, aureomycin, chloramphenicol and terramycin. There is little variation in the susceptibility of the 12 strains to the effect of any of the drugs tested.

In vivo, the therapeutic effects of the various dilutions of the agents are shown in charts A, B, C, D, E and F. In each chart a comparison of the *in vitro* reaction of the agent tested against H. parapertussis with that tested against H. pertussis is shown in the left upper area of each half of the figure. Comparison of the *in vivo* tests is indicated graphically on the right side of each half of the chart. The dose in mg./kg. body weight/day which saved 50% of the mice from death is given in parenthesis beneath the graph.

It will be observed that, under the conditions of the experiments, the range of *in vivo* susceptibility varies from 25 mg./kg. for streptomycin to 0.3 mg./kg. for polymyxin B.

The order of decreasing effectiveness against H. parapertussis *in vivo* is polymyxin B, aureomycin, terramycin, neomycin, chloramphenicol and streptomycin. Comparison with H. pertussis:

In each instance the amount of the antibiotic required to inhibit growth of 50% of the strains of H. pertussis (tables 1 and 2) is much less than that required for H. parapertussis. In the case of streptomycin the difference is particularly great. For instance, it requires 421 μg./cc. medium to inhibit growth of 50% of the cultures of H. parapertussis as compared to 2.5 μg. in the case of H. pertussis. A similar result was re-

TABLE 2

H. PERTUSSIS—SENSITIVITY TO CERTAIN ANTIBIOTICS

Antibiotic	Concentration (μg./cc. Medium) Required to Inhibit Growth of 50% of Cultures	
	Wells et al.[5]	Authors' Results
Streptomycin	7.5 (0.8–80)	2.5
Neomycin	11.0 (5–150)	3.4
Aureomycin	0.62 (0.16–12.5)	0.64
Chloramphenicol	0.51 (0.16–8.0)	0.38
Terramycin	0.43 (0.2–12.5)	0.44
Polymyxin B	0.15 (0.09–1.0)	0.06
Penicillin	0.94 (0.4–2.0)	0.91

ported by Alexander and Redman[6] who found the minimal effective concentration required for H. parapertussis to be between 100 to 200 μg./cc. as compared with 3 to 10 μg./cc. for H. pertussis.

H. pertussis is also more sensitive *in vitro* to neomycin, aureomycin, chloramphenicol, terramycin and polymyxin B and the order of susceptibility to these drugs is similar for the two organisms.

The authors' *in vitro* results with H. pertussis are compared with those of Wells and associates[5] in table 2. When the concentration of the antibiotic/cc. required to inhibit 50% of the cultures (as estimated from their published chart) is compared with that determined by the present authors, the results are remarkably similar, a finding which also speaks for the reproducibility of results for the methods used by these investigators and by the present authors were very similar.

In vivo results, as might be expected, cannot be accurately predicted for results obtained from the *in vitro* experiments in the case of either organism, although in each instance the most effective antibiotics are polymyxin B and terramycin. For instance, chloramphenicol, while fairly effective *in vitro* against both organisms is not so effective *in vivo*. However, it is moderately effective against each organism and about to the same degree. The present authors' results with chloramphenicol are somewhat at variance with those of Alexander[7] who predicted from *in vitro* tests that it might be the drug of choice in parapertussis. Further experimental work, particularly tests against the human infection, is indicated.

SUMMARY

The susceptibility of 12 strains of H. parapertussis to certain antibiotics was examined.

In vitro, the order of decreasing activity was, polymyxin B, terramycin, chloramphenicol, aureomycin, neomycin, penicillin and streptomycin. There was little variation in the response to any one antibiotic of the various strains tested.

In vivo, listed in the order of their decreasing effectiveness against the experimental murine infection were polymyxin B, aureomycin, terramycin, neomycin, chloramphenicol and streptomycin.

Compared with H. pertussis, H. parapertussis was more resistant to each antibiotic tested *in vitro. In vivo,* similar degrees of effectiveness were exhibited against the two organisms by polymyxin B, terramycin and chloramphenicol; the first two named being particularly effective both *in vitro* and *in vivo.*

ACKNOWLEDGMENT

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SPANISH ABSTRACT

La Susceptibilidad del Hemophilus Parapertussis a Ciertos Antibioticos

Sé estudio la susceptibilidad "in vitro" y "in vivo" del H. parapertussis a ciertos antibioticos.

Las pruebas "in vitro" fueron realizadas mediante el cultivo de suspensiones standard de organismos en medium de Bordet al cual concentraciones variables de antibioticos fueron añadidas previamente. Después de un período de 72 horas de incubación el grado de inhibición del cultivo fué observado.

Las pruebas "in vivo" fueron basadas en el valor protectivo de inyecciones diarias de dósis variables de antibioticos en prevenir la infección en ratones infectados con dósis standard de organismos por vía intranasal.

Sumario: La susceptibilidad de doce variedades de H. parapertussis a ciertos antibioticos fué examinada.

"In vitro" se observó el siguiente orden decresivo de efectividad antibiotica: polimixin B, terramicina, chloramphenicol, aureomicina, neomicina, penicilina y estreptomicina. No hubo variación apreciable en la repuesta de las diferentes variedades de H. parapertussis a un antibiotico en particular.

"In vivo" la efectividad antibiotica contra la infección murina experimental fué en el siguiente orden: polimixin B, aureomicina, terramicina, neomicina, chloramphenicol, y estreptomicina.

Comparado con el H. pertussis, el H. parapertussis fué mas resistente a todos los antibioticos "in vitro." "In vivo," el grado de efectividad exibido contra estos dos organismos, fué similar con el polimixin B, terramicina y chloramphenicol, los dos primeros siendo particularmente efectivos tanto "in vitro" como "in vivo."

260 Crittenden Boulevard

COAGULATION STUDIES IN THE NEWBORN INFANT

II. Erythroblastosis Fetalis

By RUTH M. HEYN, M.D., IRVING H. ROZENFELD, M.D., BURTON J. GROSSMAN, M.D., AND JAMES D. STUART, M.D.

Chicago

HEMORRHAGE as a complication of erythroblastosis fetalis has been reported. Grossman,[1] Vaughan[2] and Potter[3] refer to the occurrence of pulmonary hemorrhage in infants who have died with erythroblastosis. Autopsy reports of babies born alive and dying with erythroblastosis at the Chicago Lying-in Hospital over the past four years have shown that 50% had evidence of pulmonary hemorrhage. The observation was made by Allen and coworkers[4] that two babies with erythroblastosis had a markedly increased protamine titration. At autopsy, both babies had pulmonary hemorrhage. The present investigation was undertaken to study the possible occurrence of a coagulation disturbance in newborn infants with erythroblastosis fetalis.

METHODS

Determinations of the whole blood clotting time, prothrombin time, protamine titration, platelet count and gross observation of clot lysis were made for 10 infants with erythroblastosis fetalis within 6 hr. of birth and again on the third and fifth days of life. Eight of the 10 infants had replacement transfusions and the studies were done immediately before and after the exchange. In addition, 3 of these 8 infants had heparin sensitivity tests done before and after the transfusion. All 10 infants had positive Coombs' tests and those who had replacement transfusions had a cord hemoglobin of 13 gm./100 cc., or less.

The technics used in these determinations are described in a previous paper.[5]

RESULTS

The results obtained on the 10 infants studied are presented in table 1.

Prothrombin concentration ranged from 56% to 100% of normal in the first six hours of life. This is essentially the same as the range seen in the normal infant. In the two untreated babies (Cases 5 and 8), the serial prothrombin concentrations were within normal limits. Of the eight patients that received an exchange transfusion, six showed an elevation in the prothrombin concentration immediately after the procedure as compared to the pretransfusion level. One (Case 6) showed no change in prothrombin concentration and one (Case 7) showed a decrease from 97% to 86% of normal concentration.

On the third day of life the average prothrombin concentration in the eight transfused patients was 77% of normal, which is significantly higher than the 65% observed in the series of normal infants.[5]

By the fifth day of life all infants had 100% prothrombin concentration.

The range of the whole blood clotting time in the first six hours of life was from 7 to 56 minutes with an average of 27 minutes. The coagulation time immediately after

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TABLE 1

ERYTHROBLASTOSIS

Case	Whole Blood Clotting Time	Protamine Titration	Prothrombin Concentration	Platelets (in 1000/cmm.)	Clot Lysis	Whole Blood Clotting Time	Protamine Titration	Prothrombin Concentration	Platelets (in 1000/cmm.)	Clot Lysis	Whole Blood Clotting Time	Protamine Titration	Prothrombin Concentration	Platelets (in 1000/cmm.)	Clot Lysis	Whole Blood Clotting Time	Protamine Titration	Prothrombin Concentration	Platelets	Clot Lysis
	6 hr. (Before Transfusion)					After Transfusion					3rd Day					5th Day				
1	10′	140	71%	250	+++	11′	120	94%	358	N	6′	120	75%	234	N	5′	120	100%	—	—
2	18′	140	70%	341	N	22′	120	92%	—	N	8′	120	—	—	N	6′	120	100%	—	N
3	17′	140	56%	320	N	24′	120	92%	—	N	6′	120	76%	—	N	6′	120	100%	—	N
4	56′	>180	64%	187	+	39′	120	84%	—	N	17′	120	67%	206	N	22′	140	100%	175	N
5	32′	140	100%	295	N	No exchange					36′	120	92%	278	N	10′	140	100%	—	N
6	21′	120	68%	204	N	29′	120	68%	—	N	7′	120	82%.	150	+	27′	120	100%	—	N
7	36′	120	97%	280	N	40′	120	86%	295	N	12′	120	64%	62	N	12′	140	100%	53	N
8	7′	120	80%	207	N	No exchange					13′	120	86%	243	N	12′	120	100%	290	N
9	45′	140	81%	205	N	56′	120	94%	90	N	Died									
10	28′	120	62%	129	N	36′	120	88%	57	N	18′	120	96%	105	N	19′	120	100%	—	N

exchange transfusion ranged from 11 to 56 minutes with an average of 32 minutes. Normal infants for this age period have shown a range from 7 to 38 minutes with an average of 14 minutes.

On the third day of life the two untreated infants showed a prolongation of the whole blood clotting time as compared with the values obtained from these babies on the first day of life. In the seven treated babies the range of the whole blood clotting time was from 6 to 18 minutes with an average of 10½ minutes. Every baby in this group showed a decrease in the whole blood clotting time as compared to the pretransfusion level. The third day levels in the normal newborns ranged from 10 to 60 minutes with an average of 25 minutes.

On the fifth day of life, the whole blood clotting times in both the treated and untreated babies were comparable to the whole blood clotting times of the normal patients.

Protamine titrations, as compared to normal adult values, were found to be increased in 6 of the 10 babies (60%) within the first six hours of life. In the series of normal infants, 6 of 26 (23%) showed comparable prolongations. Five of the six infants who showed an increase in the protamine titration were transfused and in all of these the protamine titration was returned to normal immediately after the procedure.

On the third day of life all of the infants had a normal protamine titration. Seven of the 26 normal three day babies showed an increased protamine titration, as compared to normal adult values.

By the fifth day of life 3 of the 9 erythroblastic infants had an increased protamine titration. Of these three, two (Cases 4 and 7) had replacement transfusions and one (Case 5) was untreated. One of these three (Case 7) had not shown this increase previously. None of the 26 normal babies studied on the fifth day of life showed an increased protamine titration.

Heparin sensitivity tests were done pre- and post-transfusion in three of the babies (Cases 7, 9, 10). The results of these tests are shown in chart 1. It can be seen that there is no significant variation from the normal.

Gross observation for clot lysis showed no increase of lysis over what was observed in normal babies.

Discussion

The difficulties in obtaining blood from the newborn infant have been discussed in a previous paper.[5] It should be pointed out that in the erythroblastotic infants treated with replacement transfusions, the pre- and post-transfusion blood samples were drawn from the umbilical vein under ideal conditions. This, in part, may explain the higher values obtained in both of these groups for the whole blood clotting time. However, the authors feel that such high values as 45 minutes (Case 9) and 56 minutes (Case 4) for the whole blood clotting time is distinctly abnormal for the first six hours of life.

The higher levels found in the post-transfusion period, in face of a return to normal of the other coagulation factors measured, can probably be explained by the fact that small amounts of heparin were introduced intravenously into the babies during the course of the procedure. That small amounts of heparin can have this effect on the whole blood clotting time has been shown by Allen et al.[6]

The fact that the prothrombin concentration of the third day of life in the treated erythroblastotic infants is higher than the corresponding figure in the normal group is probably a result of the replacement transfusion.

The most striking observation noted was the fact that 60% of the affected infants

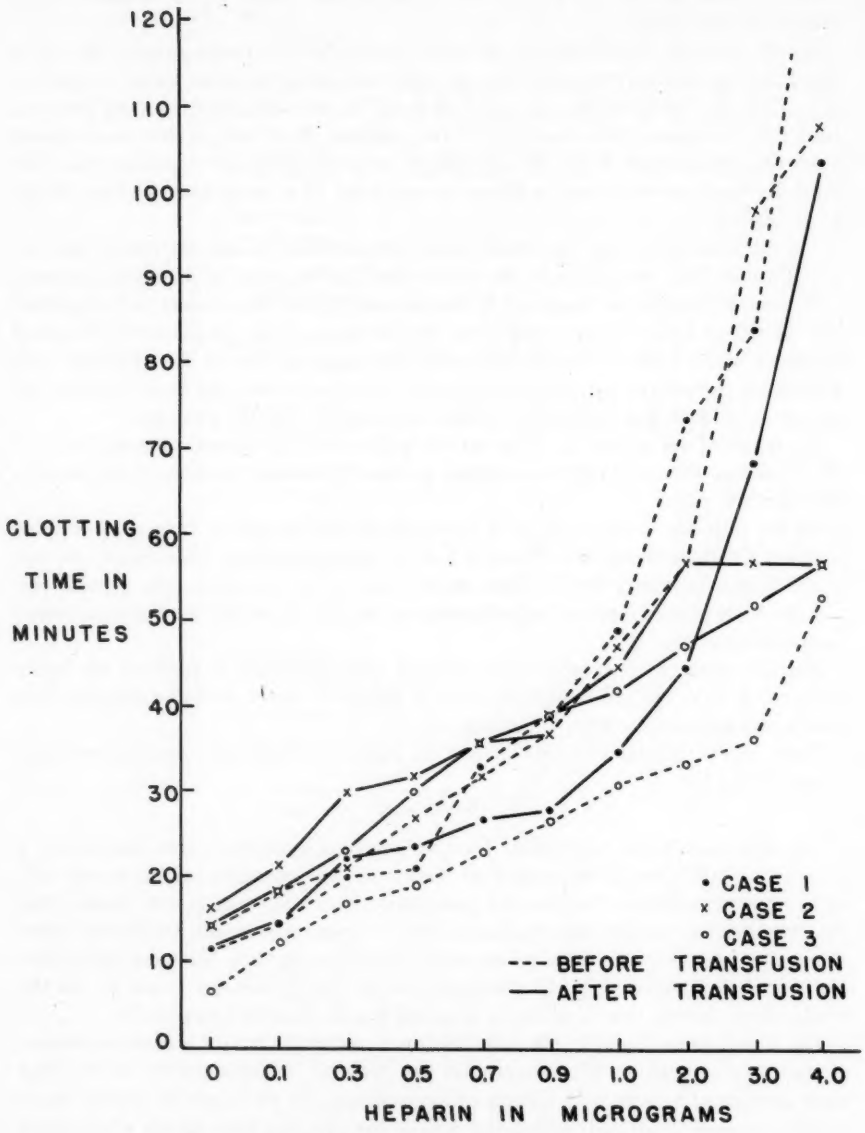

CHART 1. Heparin sensitivity curves before and after replacement transfusion.

showed an increase in the protamine titration in the first six hours of life as compared to 23% in the normal group. Case 4, with a protamine titration in excess of 180 μg. of protamine and a whole blood clotting time of 56 minutes, shows the most marked aberration from the normal. This infant had scattered petechiae at the time the above determinations were done.

Immediately following transfusion, the protamine titration returned to normal and remained so through the third day of life, but was increased in three infants on the fifth day. The values for the protamine titration differ from the values for the whole blood clotting time and prothrombin concentration in the appearance of an abnormality on the fifth day. Since the factors responsible for the increased protamine titration are not known, it is not possible to explain these findings. It is suggestive that the factors concerned with this abnormality are still active.

Of interest in this series of patients are Cases 2 and 3 which were monozygotic twins as far as can be determined by blood types and examination of the placenta.

One of the 10 cases studied (Case 9) died. This was a premature infant weighing 2010 gm., who showed progressive respiratory distress from birth on. He died on the second day of life, and autopsy revealed resorption atelectasis without pulmonary hemorrhage.

Although pulmonary hemorrhage has been found in 50% of babies dying with erythroblastosis, and although a possible coagulation defect has been shown in some of the infants studied, it cannot be concluded that this defect is the cause of the hemorrhage, since none of the babies studied developed pulmonary hemorrhage.

Conclusion

Because of the small number of cases studied, it is impossible to say that a consistent coagulation defect has been demonstrated in erythroblastosis fetalis. However, where an increased protamine titration was present, this abnormality appeared to be corrected by replacement transfusion.

It is not possible to conclude from the data obtained that this coagulation disturbance is the cause of pulmonary hemorrhage in erythroblastosis since none of these infants revealed any evidence of pulmonary hemorrhage.

Summary

Determinations of the whole blood clotting time, prothrombin concentration, protamine titration, platelet count, and clot lysis were done on 10 infants with erythroblastosis fetalis on the first, third and fifth days of life.

On the first day of life the average whole blood clotting time was 27 minutes as compared to an average of 14 minutes in the normal infant. The protamine titration was increased beyond normal adult values in 60% of the infants as compared with 23% of normal infants. The prothrombin concentration was comparable to that of the normal infant.

Eight of these infants received replacement transfusions and repeat determinations of the above factors immediately after transfusion showed a return to normal of the protamine titration.

Heparin sensitivity tests done on three of the treated infants before and after transfusion were essentially normal.

On the third day of life the average whole blood clotting time was 10½ minutes in

the treated infants as contrasted with 25 minutes in the normal infant. Protamine titrations were normal in all infants. The average prothrombin concentration was 77% as compared with 65% in the normal three day infant.

On the fifth day of life all determinations were normal except for those from three infants who had increased protamine titrations.

ACKNOWLEDGMENTS

The authors wish to express their appreciation for the support and encouragement given by Dr. Mila Pierce, Associate Professor of Pediatrics, University of Chicago.

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SPANISH ABSTRACT

Estudios de la Coagulación de la Sangre en Recién Nacidos
II. Eritroblastosis Fetalis

Determinaciones del tiempo de coagulación de la sangre total, concentración de protombina, titración de protamina, contaje de plaquetas y observación visual de la retracción del coagulo, fueron hechas en diez niños con eritroblastosis fetalis durante el primer, tercer y quinto día de nacidos, y estos resultados fueron comparados con data similar obtenida en niños normales.

Durante el primer día de nacido, los pacientes con eritroblastosis fetalis presentaron un tiempo de coagulación prolongado y un aumento de la titración de protamina en relación a los niños normales, mientras que los resultados en la concentración de protombina, contaje de plaquetas y retracción del coagulo fueron comparables a los obtenidos en el grupo de recién nacidos normales.

920 East 59th Street

Pediatrics

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AMERICAN ACADEMY OF PEDIATRICS, INC. PROCEEDINGS AND REPORTS

THE PRESIDENT'S PAGE

THIS is about the time of year when good business men take inventory of stocks on hand, balance assets against liabilities, and attempt to formulate a program which will guide them in the months to come. Sober, realistic appraisal of recent trends in medicine necessarily includes consideration of the rapidly growing medical care plans which are being developed throughout this country and Canada. It is very proper for us as physicians to acquaint ourselves with the details, methods of administration and comparative advantages of the various proposed programs. Voluntary health insurance is one of the answers to recent agitation concerning a National Compulsory Health program. Our patients have a right to expect of us a reasonable familiarity with the practical application of these insurance plans; and to warn them concerning pitfalls which lurk in the fine print on the policy. The informed, conscientious physician constitutes the best safeguard in attempting to keep insurance costs reasonable. Abuses of health insurance only raise the cost of protection. Increasing demands upon income require adequate protection for those who need medical and surgical care on a budget basis at a price they can afford. Too often the economic shock of prolonged, serious illness places terrific strain upon the financial reserves of a family. It is logical to assume that better medical care for more people can most efficiently be administered in a system of free enterprise and in accordance with traditions of our American way of life. An alternative plan has been proposed by those who advocate government operated medical care; and who would enact legislation making such a program the law of the land. The latter has been described as the "allotment of an unknown sum for an unpredictable purpose."

Budgeted health programs under voluntary systems provide an opportunity to purchase insurance for all or any part of medical and hospital bills. They can be modified in many ways according to individual needs. Currently there are 92 separate plans with more than 10 million members, sponsored by the American Medical Association and the various State Medical Societies. In addition, there are commercial and industrial plans, fraternal programs and private group clinics with prepayment systems.

But the case of voluntary health insurance has been argued more convincingly by those better qualified to speak upon such a subject. The purpose of these paragraphs is to emphasize the obvious fact that, under the provisions of these various plans, the physi-

cian must conform to certain regulations which directly affect his practice and the fees which he can collect. "Something new has been added." Very few of us have the opportunity to study the advantages of one program over another.

The Executive Board at its meeting in October 1951 directed your President to appoint a special committee for the Study of Medical Care and Insurance Plans in the United States and Canada. This formidable title is in keeping with the task to be accomplished. It is realized that an objective, unbiased evaluation of plans for voluntary medical care insurance and for different methods of providing service is very important information for the Academy membership.

The personnel of this Committee is listed below. You will note that it is nation-wide in scope; and is composed of members whose business acumen, sagacity and mature judgment will add much to their deliberations. They are already enthusiastically at work on their important task. If you have comments or suggestions, communicate with the Chairman, Dr. Edward A. Wishropp, who is also the Academy Liaison Representative to the National Blue Shield Medical Care Plans.

COMMITTEE

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Recently it has been estimated that about 80 million Americans are now protected by some form of voluntary health insurance. Inexpensive, comprehensive protection, available on a sound medical and financial basis to every American who wants it—that is the objective! And it has a direct personal effect upon you and me. Help your Committee to do a constructive job! A report of their study will be given at the Annual Meeting this fall in Chicago.

WARREN W. QUILLIAN, M.D., *President*

SUPPLEMENTARY REPORT OF THE COMMITTEE ON IMMUNIZATION AND THERAPEUTIC PROCEDURES FOR ACUTE INFECTIOUS DISEASES

NOVEMBER 26, 1951

AT a meeting of the Committee held in Toronto on October 22, 1951, the evidence associating immunization procedures with paralytic poliomyelitis was reviewed. The information (published and unpublished) which is available at present is insufficient to conclude whether injections of vaccine and/or toxoid, and also possibly smallpox vaccination, predispose to paralytic poliomyelitis. The members of this Committee therefore are not able to alter the views expressed in their report of May 1951 which was published in the recent (1951) edition of the *Red Book* (page 2, paragraph 3 and page 50, paragraph 7). However, as there have been numerous requests for amplification of these views, the following recommendations are submitted:

It is recommended that immunization procedures be not discontinued on a seasonal basis in anticipation of an epidemic. When, however, an outbreak of poliomyelitis of considerable proportion occurs in one's community, then elective immunization procedures in individuals over the age of six months should be deferred. Elective procedures are considered to be (1) primary and routine recall injections of tetanus toxoid, (2) primary and routine recall injections of diphtheria toxoid, pertussis vaccine, and typhoid vaccine in the absence of existing diphtheria, pertussis, and typhoid, respectively, in the community, and (3) primary smallpox vaccination and revaccination in the absence of any cases of smallpox. If outbreaks of any of these diseases coexist in the community with an outbreak of poliomyelitis the above immunization procedures would cease to be elective and should be performed: that is, unprotected children should be given their primary immunization and previously immunized children should receive a recall injection of the appropriate antigen. "Wound boosters" of tetanus toxoid following wounding should never be deferred even in contacts to poliomyelitis cases.

This Committee has advised that primary immunization against diphtheria, pertussis and tetanus be commenced with combined antigens at three months of age. It is therefore generally possible to finish the job and also to include smallpox vaccination before the age of six months. Because of the rarity of infantile paralysis in infants under six months of age it is recommended that these procedures be followed regardless of the presence of an outbreak of poliomyelitis in the community.

As the evidence relating paralytic poliomyelitis to injections of penicillin is very fragmentary the Committee does not wish to revise its previous statement with respect to this agent. The indications for penicillin injections almost always transcend any potential danger therefrom. However, when contacts to known cases of poliomyelitis require penicillin it is recommended that oral administration be employed unless circumstances dictate the intramuscular route. This is in keeping with the desire to minimize trauma in exposed individuals.

As the evidence relating paralytic poliomyelitis to injections of hormones, pollen antigens, house dust extracts, etc., is even more tenuous than that implicating penicillin, the Committee feels that parenteral administration of these agents should not be discontinued except in known contacts to cases of poliomyelitis.

In view of the possibility that occasional cases of poliomyelitis following an immunizing injection may conceivably be due to the introduction of the virus through the skin, the importance of adequate skin sterilization is re-emphasized. Two per cent tincture of iodin is probably the most effective agent.

When in the future an etiologic relationship between injection of immunizing agents and paralytic poliomyelitis is established or is disproven, then it will be possible to formulate more definite guides for conducting immunization and reimmunization procedures.

CORRECTION OF SUMMARY ON RABIES IN 1951—REPORT OF THE ACADEMY COMMITTEE ON IMMUNIZATION AND THERAPEUTIC PROCEDURES FOR ACUTE INFECTIOUS DISEASES

ATTENTION is called to pages 53 and 54 of the 1951 report of the above committee (the *Red Book*). The recommended antirabies serum (Sheep-Lederle) has been withheld by the manufacturers because of allergic reactions accompanying the use of this product. Unfortunately no other rabies antiserum is commercially available at present. Active immunization with rabies vaccine (the Pasteur treatment) remains the sole biologic weapon in rabies prophylaxis in addition to the highly important care of the wound.

The indications for the use of phenolized (Semple type) vaccine are given in the summary. Furthermore, in view of the fact that an antiserum is not now commercially available, an additional indication must be mentioned.

When a child who has had rabies vaccine in the past is re-exposed, the danger of rabies must be balanced against the great risk of inducing treatment paralysis with a second course of vaccine. Sensitization to brain tissue proteins is very likely to exist in such individuals and the rate of neuroparalytic accidents is high. Therefore (in the absence of available antiserum) when a re-exposure with a head, neck, or hand bite occurs a recall series of vaccine injections not to exceed six doses is recommended. The appearance of any sign of a systemic reaction, such as tingling of the extremities, girdle pains, headache, nausea, sphincter disturbances or fever, is a signal for discontinuing vaccine injections.

It should also be noted (page 54) that whereas antirabies serum was recommended in instances of salivary contamination of abraded skin in the absence of teeth marks, Pasteur treatment is not recommended in this situation. Here the risks of treatment outweigh the risks of rabies.

The potential dangers of the Pasteur treatment, particularly in previously sensitized individuals, give rise to hope that a potent antiserum will be available soon.

ERRATUM

Page 31. Infectious (Epidemic) Hepatitis- #7, fourth line; Sentence beginning "Dosage is 0.025 cc per kg body weight" should read "Dosage is 0.25 cc per kg body weight."

ACTH, CORTISONE AND ALLIED SUBJECTS

A Symposium

JEROME W. CONN, M.D., *Chairman*
University of Michigan School of Medicine, Ann Arbor, Mich.

PHARMACOLOGY AND PHYSIOLOGICAL ACTION OF ACTH, CORTISONE AND ALLIED SUBSTANCES ON BODY FUNCTION

(Abstract not available)

JEROME W. CONN, M.D.

TREATMENT OF CONGENITAL ADRENAL HYPERPLASIA WITH CORTISONE

LAWSON WILKINS, M.D.
Johns Hopkins University School of Medicine, Baltimore

INFLUENCE OF ACTH AND CORTISONE ON INTROGEN AND CALCIUM BALANCES IN CERTAIN DISEASE STATES

(Abstract not available)

JOSEPH A. JOHNSTON, M.D.
Henry Ford Hospital, Detroit

EXPERIENCES WITH ACTH IN THE TREATMENT OF THE ACUTE PHASE OF RETROLENTAL FIBROPLASIA IN PREMATURE INFANTS

FREDERICK C. BLODI, M.D., ALGERNON B. REESE, M.D., WILLIAM A. SILVERMAN, M.D., AND RICHARD DAY, M.D.
Institute of Ophthalmology and the Babies Hospital, Columbia-Presbyterian Medical Center, New York

INFLUENCE OF ACTH AND CORTISONE ON LEUKEMIA

JOHN E. FRANKLIN, M.D.
Memorial Hospital, New York City

EFFECT OF ACTH IN CHILDREN WITH THE NEPHROTIC SYNDROME

HENRY L. BARNETT, M.D.
University Medical College, New York City

EFFECTS OF ACTH AND CORTISONE ON ASTHMA AND ECZEMA

JEROME GLASER, M.D.
University of Rochester School of Medicine and Dentistry, Rochester, N.Y.

INFLUENCE OF ACTH AND CORTISONE ON RHEUMATIC FEVER

(Abstract not available)

JOHN D. KEITH, M.D.
Hospital for Sick Children, Toronto

Presented at the Annual Meeting of the American Academy of Pediatrics, Toronto, Oct. 25, 1951

TREATMENT OF CONGENITAL ADRENAL HYPERPLASIA WITH CORTISONE

LAWSON WILKINS, M.D.

Congenital adrenal hyperplasia in females causes pseudohermaphroditism which must be differentiated on the one hand from various types of genetic intersexuality and on the other from virilization due to adrenal tumor. In males it causes macrogenitosomia precox which must be differentiated from other types of sexual precocity and from adrenal tumor. The major manifestations of the disorder are due to the excessive secretion of adrenal androgen which causes progressive virilization throughout embryonic and postnatal life. In some cases there is a defect of electrolyte regulation which may lead to death with Addisonian symptoms or heart block.

Partial adrenalectomy and the administration of estrogens or inert androgens have failed to check the progressive virilization, but cortisone has succeeded in doing so by suppressing the excessive activity of the abnormal adrenals. This effect of cortisone can be accomplished with small doses which do not exceed physiologic requirements, whereas in the treatment of hypersensitivity states and various other conditions large doses of cortisone are required for its pharmacodynamic action.

We have now treated 11 patients continuously for periods of 6 to 17 months without ill effects. It is important to determine in each case the minimum dose required to maintain adequate suppression of the adrenals. This is measured by the level of urinary 17 ketosteroids. In patients over 8 years the ketosteroid excretion should be maintained below 8 mg. per day (preferably 4 to 6 mg. per day) and in young infants at 0.5 to 1.5 mg. per day. This degree of suppression can be brought about rapidly in older children by the administration of 25 to 50 mg. of intramuscular cortisone daily. After suppression is attained, it may be maintained indefinitely in the older children by 25 mg. of intramuscular cortisone daily, or 75 mg. every third day. With oral cortisone 50 to 75 mg. (given in 3 divided doses) are required. Young infants probably require a maintenance dose of 5 to 10 mg. of intramuscular cortisone daily, or 2 or 3 times this amount of oral cortisone.

In 6 female pseudohermaphrodites 8 years and older who were treated there was definite decrease of hirsutism and other signs of virilization. All of them developed breasts and estrinization of the vaginal smears, and 3 have menstruated regularly. With the doses used there have been no changes in carbohydrate metabolism and no other manifestations due to excessive cortisone.

The infants treated have shown no progressive virilization. It is important to follow their rates of growth and osseous development. An excessive amount of cortisone may inhibit growth and development. With proper doses, however, suppression of adrenal androgen may be maintained without inhibiting normal growth and development.

Infants with congenital adrenal hyperplasia who have defective electrolyte regulation must be treated with a high Na intake and/or desoxycorticosterone in addition to cortisone.

It seems probable that cortisone therapy will have to be continued indefinitely. Even after treatment has been continued for as long as a year, the overactivity of the adrenal has returned on withdrawing cortisone. During treatment slight infections and other stresses have caused temporary increases of adrenal activity as measured by the ketosteroid excretion.

To reiterate, in order to obtain satisfactory clinical results it is necessary in each case to determine the minimum dose of cortisone required to maintain adequate suppression of the urinary 17 ketosteroids. The maintenance dose of oral cortisone required is 2 or 3 times that of intramuscular cortisone. With proper dosage no abnormal metabolic or toxic effects of cortisone have been encountered.

EXPERIENCES WITH ACTH IN THE TREATMENT OF THE ACUTE PHASE OF RETROLENTAL FIBROPLASIA IN PREMATURE INFANTS

FREDERICK C. BLODI, M.D., ALGERNON B. REESE, M.D., WILLIAM A. SILVERMAN, M.D., AND RICHARD DAY, M.D.

During 1950 a trial of ACTH for 2 or 3 weeks during the acute phase of retrolental fibroplasia in premature infants yielded encouraging results. The number of infants progressing to partial or complete blindness in the hospital where ACTH was used was less than in the hospital where it was not used. During 1951 the treated and untreated infants were in the same nursery and were chosen

by lot. The treated infants did slightly, though not significantly, worse than the untreated. In the table presented below the results are given for both years combined. Only cases progressing to the stage of distinct peripheral retinal edema are included. The conclusion is that ACTH is not proved to be of benefit in this condition. The treatment schedule followed led directly to 2 deaths, and indirectly to 4 others.

	No. of eyes with adequate vision	Eyes with no vision	Indeterminate
Treated	41	14	9
Not treated	29	17	4

INFLUENCE OF ACTH AND CORTISONE ON LEUKEMIA

JOHN E. FRANKLIN, M.D.

On the Pediatric Service of Memorial Hospital there have been 44 cases of acute leukemia, from December 1949 to August 1951, which have been treated with ACTH and cortisone. These studies were done under the supervision of Drs. Pearson and Burchenal of the Sloan-Kettering Institute and were undertaken because of the effect of these hormones on lymphoid tissue and producing remissions in leukemia in mice (Lau and Speirs). These cases were all in children ranging between 6 months and 14 years of age. They all fall under the classification of acute leukemia without any further breakdown. Many attempts to establish an accurate classification of leukemia in children were made without success. In the leukemia clinic it is felt that 5% of the patients can readily be classified as myelogenous leukemia, 45% as lymphatic and granulocytic leukemia and the remaining 50% fall into that group diagnosed with difficulty even by expert hematologists. After finding that our hematologist disagreed as to the classification of many of these cases, slides were sent to outstanding hematologists with resulting disagreement among them.

Except where treatment failed, subjective improvement was noted during the first weeks characterized by a sense of well being and improvement in appetite. Most of these children developed a voracious appetite and in the first cases treated 3 and 4 servings at each meal were not unusual. As a result there was a marked and continued increase in their weight. Edema, the result of electrolyte imbalance, developed later. Subsequently, this was controlled by limiting the diet to 1200 to 1600 calories per day with 40 to 60 gm. of protein and a low salt intake. Some of these cases showed an alkalosis, a decrease in potassium and cardiac irregularities. The giving of potassium salts by mouth corrected the potassium deficiency and relieved these secondary symptoms, namely, apathy, lethargy, muscular weakness, paralysis, abdominal distention and cardiac irregularities. Glycosuria was found on occasion in moderate degrees and diabetes developed in one patient requiring treatment and persisting through the remaining course of the disease.

Where treatment was able to be maintained there was usually a slow but gradual development of a Cushing's syndrome, manifested by a moon-face, large torso, especially enlargement of the abdomen, thinning of the arms and legs, acne and a sense of general well being. In addition there was a shrinkage in the size of the enlarged lymph nodes, and a decrease in size of the enlarged livers and spleens. Bleeding from the nose, bowel, urinary tract and skin ceased early in those successfully treated. I.V. ACTH, 30 mg. a day, has been very dramatic in controlling bleeding.

Early changes in the hematologic picture occurred during the first week with the WBC starting to return to their normal numbers—if elevated—and with an increase in their maturity. An increase in the number of reticulocytes occurred between the 7th to 14th day, reaching a peak of 10 to 20% during the 2nd and 3rd week of therapy. Platelets increased between the 7th and 21st days.

During the 2nd and 3rd week of treatment there was manifestation of improvement in the bone marrow by an increase in erythropoietic activity. During this time there could be an increased maturity of the myeloid cells and a decrease in percentage of the leukemic cells. In none of the patients was there a complete disappearance of abnormal cells from the bone marrow or peripheral blood.

None of the above reactions interfered with continued treatment. The serious complications which did cause cessation of the treatment were:

1. Pyogenic infections—lowered resistance to infections have previously been noted in Cushing's syndrome. Skin infection, abscesses, otitis media, tonsillitis and pneumonia were common complications in these cases with acute leukemia and required the constant administration of one of the antibiotics.

2. Hypertension was by far the most serious complication we encountered occurring in 15 patients or 34.9%. Ten of these 15 cases developed cerebral symptoms consisting of headache, stiff neck, listlessness, vomiting, twitchings, convulsions or coma. Most of these patients developed symptoms rapidly and all but 5 lost these slowly following cessation of treatment. One patient was readmitted 16 days after discharge with convulsions, coma and hypertension during which time he had received no treatment with these hormones. The following slide shows us that there was: (a) one patient who died with clinical signs of cerebral hemorrhage; (b) another who had grossly bloody spinal fluid on L.P.; (c) 2 patients where hemorrhage plus softening of the brain were found at autopsy; (d) one patient where autopsy showed cerebral edema; (e) additional case with cerebral symptoms that showed cerebral abscesses on autopsy. These complications occurred on both cortisone and ACTH and developed anywhere between the 2nd and 41st day of treatment. Cortisone was used in 8 and ACTH in 7 cases. Subsequent treatment with cortisone produced a recurrence of the signs in 2 and was without effect in 2 other cases (ACTH produced signs in 5th). In the cases first treated with ACTH cortisone reproduced symptoms in one and had no effect in another case.

Complete remissions of this disease has not, in our experience, appeared to be obtainable with these hormones. They are usually of short duration and resistance to hormone therapy develops rapidly. Remissions were considered good when there was loss of fever, cessation of bleeding or hemorrhagic tendencies, general well being plus reduction in size of the liver, spleen and lymph nodes. In addition the bone marrow showed an increase in the erythroid elements and there was a marked reduction in the percentage of leukemia cells. A partial remission was considered when the above factors were found with only a partial reduction in the leukemic cells.

In our series of 44 cases there were 17 female and 27 male children between the ages of 6 months and 14 years. Twelve cases had received no previous treatment but the response was similar to the remaining 32 cases that had been treated and had become resistant to various drugs such as 2,6 diaminopurine, A-methopterin, aminopterin, glyoxylide and urethane. The dosage of ACTH varied between 20 to 100 mg. per day and of cortisone between 50 to 200 mg. per day depending on the age of the patient and response to therapy.

Twenty-four cases or 54.5% showed remissions and there were 20 failures. Fifteen or 60% out of 25 cases treated with cortisone had remissions. Nine or 47.7% out of 19 cases treated with ACTH had remissions. There were 16 good remissions and 8 partial remissions. These lasted from a minimum of 16 days to a maximum of 135 days, averaging 48.5 days. The number of days of treatment in the remissions varied from 8 to 86 days and averaged 26.9 days. The average dose of ACTH was 61.7 mg. and cortisone 130.2 mg. per day.

The partial remissions lasted 6 to 21 days and were treated for a larger period of time and with a greater amount of medication. The average number of days of treatment was 73 (40 days for cortisone and 33 days with ACTH, which averaged 36.5 days), while the average dose was 160.9 mg. of cortisone and 65 mg. per day of ACTH.

In the 20 failures the number of days of treatment averaged 23.1 days with ACTH and 24.4 days with cortisone while the average daily dose was 59.5 mg. of ACTH and 154.4 mg. of cortisone daily.

A summary of these failures show that: (1) 6 cases were treated 8 days or less; (2) one died in cardiac failure in 4 days; (3) one died from a pericardial tap; (4) one had medication stopped following convulsions; (5) 11 were adequately treated.

There were 18 cases treated 2 or more times and a response was obtained in 7 or 38.8%. The average length of these remissions in second courses of treatment was 33.3 days. In all cases but one the hormones had to be given in larger doses and for a longer period of time before a remission was obtained. Many patients who showed an initial response to the treatment failed to show any beneficial response on a second trial and many died while hormone therapy was being administered.

In conclusion these hormones are a useful aid in the treatment of acute leukemias of childhood. ACTH appears to have the more rapid action and is therefore more useful in the acutely ill child. Cortisone, on the other hand, appears to be more effective in our series. Hypertension with cerebral symptoms is a serious complication that must be constantly watched for and treatment discontinued when these signs and symptoms appear. The response to these hormones is as good in the cases

resistant to antifolic antagonists as in untreated cases and it has been found that the antifolic antagonists are just as effective in cases that have become resistant to these hormones. Consequently, our present treatment at Memorial Hospital consists of the use of the antifolic drugs when the diagnosis of acute leukemia is just made until the resistance to these drugs develops. These hormones are saved for a probable relapse when again these patients may respond to the antifolic treatment, with a good chance that a second partial remission can later be obtained with these hormones.

EFFECT OF ACTH IN CHILDREN WITH THE NEPHROTIC SYNDROME

HENRY L. BARNETT, M.D.

It has been demonstrated recently that several agents are capable of inducing abrupt, profuse, and sustained diuresis in children with the nephrotic syndrome. These dramatic events are clinically similar to the diureses which occur spontaneously. At the present time ACTH appears to be the most satisfactory means of inducing such diureses. Diureses occur in about 80% of children given a single course of ACTH. Following such induced diureses, there may be (a) almost immediate reaccumulation of edema, (b) a variable period of clinical remission with later exacerbation or (c) occasionally complete healing. If there is reaccumulation of edema, diuresis may occur with later courses of ACTH. On the other hand, a child who responds to one or two courses may fail to respond subsequently. Finally, failure to respond to the first course does not preclude subsequent responses.

ACTH, in a dosage of 50 mg. per 24 hours given intramuscularly in 4 divided doses for periods ranging from 8 to 12 days, induces diuresis as regularly as in larger doses. However, smaller daily or total dosages given intramuscularly are usually ineffective.

Complications of ACTH administration in children with the nephrotic syndrome include: 1. metabolic disturbances: hypotonicity of the extracellular fluid accompanied by low serum potassium, alkalosis, and tetany may occur. The potassium content of the diet should be increased in an attempt to prevent this complication. 2. Infections: The administration of ACTH may mask signs of the serious infections which are so common in these children. Prophylactic antibiotic therapy is given routinely during ACTH administration. 3. Cardiovascular complications: Progressive elevation of blood pressure or increase in a pre-existing hypertension may require cessation of ACTH administration. 4. Hyperadrenocorticism: During short courses of treatment physical and metabolic signs of Cushing's disease usually do not appear. However, they may be seen if children are treated longer than 14 days or when repeated courses are given at short intervals. These changes disappear following cessation of ACTH administration.

There is no evidence that changes which accompany or follow diureses induced by ACTH differ in any respect from those accompanying spontaneous or other types of induced diuresis. The demonstration that proteinuria and hyperlipemia are decreased and filtration rate may be increased after diureses leads us to attach more than symptomatic importance to these events and to believe they should be induced. However, on the principle that hormonal therapy should not be given unless clearly indicated, we believe patients should be given a chance to have a spontaneous diuresis before receiving ACTH. Our present practice is to withhold ACTH for 6 to 8 weeks after the onset of the disease or of an exacerbation. If a spontaneous diuresis has not occurred by this time, and particularly if reduced renal clearances are found, we advise giving ACTH.

It is obviously difficult to evaluate the true importance of agents such as ACTH. Although at present it must be doubted that the eventual course of the nephrotic syndrome is altered by the administration of ACTH, the ability to induce sustained diureses followed by variable periods of remission permits at least symptomatic benefit and has facilitated important observations hitherto not practicable. It can be hoped that such observations will lead to greater understanding of the mechanisms of the disease.

INFLUENCE OF ACTH AND CORTISONE ON ASTHMA AND ECZEMA

JEROME GLASER, M.D.

Five infants and children, 2 boys and 3 girls, suffering from atopic dermatitis and varying in age from 6 months to 14 years were treated with ACTH or cortisone. All responded favorably to treatment but relapsed when this was discontinued. In no case did the skin ever return completely to normal but the improvement was highly satisfactory both from the standpoint of appearance and relief of pruritis. The skin could be cleared sufficiently so that direct testing could be done which in every instance corroborated the results of previous passive transfer tests. There were 2 instances in which the treatment was accompanied by complications. A 2 year old girl, who also had minimal pulmonary stenosis, the only symptom of which was a murmur, developed hypertension which disappeared when the dose of ACTH was reduced. A 1½ year old boy developed mild but typical nephrosis during the second week of treatment with ACTH. This suggests that ACTH, which is often employed satisfactorily for producing diuresis in nephrosis, probably has no influence on the etiologic factors in this disease. One adolescent girl with a severe mental depression caused by the disfiguration of eczema responded very well to cortisone treatment both as regards the psychosis and the eczema. All patients, except the boy with nephrosis, gradually improved under orthodox management after the hormone therapy was discontinued. A 2½ per cent cortisone ointment was found ineffective in the local treatment of eczema. The rebound phenomenon, i.e., recurrence of the eczema in a more severe form after cessation of therapy, was not observed.

There were 8 children with intractable perennial asthma, 2 boys and 6 girls, ranging in age from 19 months to 14 years. In 2 asthma had started at the ages of 3 and 4 months, respectively. All cleared under ACTH or cortisone therapy with remissions varying from 24 hours to 3 months. Occasionally these patients had relapses of sufficient severity as to require second and third courses of ACTH or cortisone. Three were continued at home on ambulatory therapy. One girl, after 76 days of ambulatory therapy, developed a typical Cushing's syndrome which disappeared in the course of 3 months after hormone therapy was discontinued.

There were 4 additional children, all under 5 years of age, who had frequent severe asthmatic attacks at home, not bad enough to require hospitalization often, but severe enough to require frequent injections of epinephrine. These children were carried along on occasional ambulatory courses of ACTH. One of these, a 3 year old, has done very well on a dose of 5 mg. daily.

So far as is known at present, both ACTH and cortisone produce the same effects in eczema and asthma. We used ACTH more often than cortisone because it was less expensive and more readily available. These drugs should be used only when the disease is severe enough to cause symptoms imperatively demanding relief which the patient has been unable to secure from any other form of therapy.

Round Table Discussion

SPEECH DEFECTS IN CHILDREN

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Chairman Bloomer: In leading this round table I have with me Dr. Charles Strother, Professor of Clinical Psychology in the College of Medicine of the University of Washington at Seattle. I am from the University of Michigan Speech Clinic in Ann Arbor. We are very glad to be with you at this round table because it suggests the close relationship between the fields of speech pathology and pediatrics.

We come to the American Academy of Pediatrics as representatives of the American Speech and Hearing Association which is the national organization for professional people interested in the study of speech disorders, their causes and their methods of treatment. Perhaps you are familiar with the official publication of the Association, the *Journal of Speech and Hearing Disorders.* We bring you greetings from the Association.

I think you may be interested in a brief outline of our general plan of discussion for the afternoon. The first part of our discussion will review the importance of a knowledge of speech disorders to specialists in pediatrics. Next we shall discuss in some detail the nature of these disorders and the etiologic factors which are frequently encountered, and then we shall suggest methods for handling the speech problems which the individual child may present. We shall be glad to have your participation, your questions, and your comments at any time during our discussion.

We feel that this subject is particularly timely because of the steadily increasing interest of pediatricians in the general aspects of child growth and development rather than in only the medical care of children. Certainly we must concede that the development of speech is fundamental to normal growth, and is highly dependent upon the physical and environmental circumstances which are the proper concern of pediatric practice.

In suggesting the basis for the modern study and treatment of speech disorders there are 2 principles that I wish to state for you this afternoon. The first is that normal speech is a function of normal physical development, normal personality and an environment conducive to the learning and expression of language. I think we don't need to elaborate that postulate a great deal; we pretty well accept the notion that the normal child learns to talk normally. We accept also the idea that speech is a learned activity and that anything which interferes with the normal course of learning speech or language is destined to leave a permanent trace unless special means are instituted for correcting it.

The second point that I bring to your attention is that speech is essential to normal personal development. There are at least 4 ways in which speech influences the development of the individual. First of all, and this is quite important, speech affects the child's own evaluation of himself. If his speech is deficient and is thus evaluated by the child it often leads him to feelings of inferiority. Speech is a highly personal thing, one of the most personal things about us, and we are all well aware of the degree to which people judge us by our speech. Second, our speech affects not only our evaluation of ourselves but it has economic implications because it bears on our employment opportunities. There are many instances of people who have achieved success partly because of their superior ability in speech, and many instances of failure because of inability to use speech effectively. Third, the ability to speak partly determines our social status. This influence is frequently noted in our clinical practice and in our observation of school children. Children, in their selection of friends, tend to reject those children whose behavior, whether speech behavior or other behavior, deviates unacceptably from the average. There is a clear tendency for children to reject the child whose speech is abnormal. A fourth way in which speech proficiency affects the individual is in the field of educational advancement. To a large extent our willingness to persevere toward educational goals

is dependent on our success in handling speech. Many a speech defective child or adult has quit school to avoid the humiliation of class recitations.

If we are to agree that speech is so important in personal development, it is logical at this point to ask how speech is acquired and by what stages it is acquired. Many of you are well aware of these things but it may be helpful to review them briefly.

First of all, the normal development of chewing, sucking, swallowing and breathing are basic to the acquisition of normal speech patterns. If those physiologic processes are disturbed in a child we are likely to find disturbances in his speech development. The natural drives of the child toward communication are conditioned also by such environmental circumstances as the stimulation from adults and particularly by the mother-child relationship with its noticeable effects on emotional life. It is extremely important for speech development that all of these processes should develop in an atmosphere which is physically and emotionally healthy. The age at which children begin to use speech and the success with which they achieve the use of speech depends a great deal upon early health, early feeding experiences, and the parent-child relationships established in the first year or 2 of growth.

The stages of development for the acquisition of speech are briefly these: Although speech is said to begin with the birth cry, crying is a rather nonspecific kind of behavior which I suspect provides very little basis for speech. Most speech probably develops out of the vocal play which begins and is more or less continually elaborated during the early months of life. Vocal play is observed not only with the normal child but also with the deaf child. Vocal play will not persist, however, or develop into more complex forms unless the child's hearing is intact. Somewhere between the ages of about 9 months to 2 years the child begins to use words to express meaning. It is in this highly experimental stage that the child begins to use speech to manipulate his environment and goes through those endless activities in commanding obedience from his elders which are at once the delight and the exhaustion of his parents.

Somewhere between 1 and 3 years of age the average child begins to make use of sentences and to develop sentence structure and vocabulary appropriate to the situation.

It should be borne in mind here that when we speak of speech and language we are talking about a function which has at least 3 major uses. It is the child's means of enlarging his intellectual sphere because through it he can manipulate symbols rather than things. It also provides his main means of social control. The world is magic for the small child and a good deal of that magic is accomplished by being able to vocally express his needs. Language further serves the very useful purpose of letting other people know about his internal state, and as such it does a great deal to relieve his internal tensions. It thus becomes a means of great emotional release as the child develops more specific use of language, and of course, its misuse can greatly complicate his emotional life.

From this extremely condensed overview of the development of language, the uses of language, and the effects which language has upon personal growth and development in the child we can easily draw the conclusion that speech is a complex process subject to many influences and in turn capable of exerting influence on many aspects of well being in the child. It is thus important for us to consider the means by which speech may become aberrant.

Dr. Charles Strother, Seattle: I would like to stress what Dr. Bloomer has said about the complexity of speech. It is probably the most complex physical skill we ever acquire. It involves, of course, a great deal more than simply skill in the muscle movements that are involved. It assumes, in the first place, a reasonably normal speech structure. If there is an abnormality of the palate, for example, deviations in speech are almost certain to occur. Not only is a reasonably intact physical structure necessary but we need to remember that speech is what we call an overlaid, or learned, function. Strictly speaking, there is no such thing as a speech mechanism. We simply utilize for purposes of speech the mechanisms of respiration, mastication and so on. Speech is also dependent on the intellectual development of the child, on his emotional development, and to an important extent on the social environment in which he develops. This statement might constitute an outline for an etiologic classification of speech disorders. We are accustomed to differentiate disorders which are due to organic causes, disorders which are due to disturbances in the development of personality, disorders that are due to difficulties in intellectual development and finally disorders that are a consequence of an abnormal social environment.

Because so many factors enter into speech and because it is a relatively complex function, difficulties frequently occur. Speech disorders have a high incidence among children. The estimates differ according to the criteria one wants to apply but range anywhere from 1% to 22%. I think a conservative

estimate would be that between 5 and 7% suffer disorders due to speech that are of clinical significance.

These disorders present themselves in pediatric practice in a number of forms. My own experience in the Department of Pediatrics at the University of Iowa and at the Childrens Orthopedic Hospital in Seattle indicates that a considerable number of children coming in to out-clinics or private offices are brought in either primarily or secondarily as a consequence of speech difficulty. The severe organic disorders of cleft palate and the speech disorders of cerebral palsy present themselves very early; parents become worried about speech retardation if the child hasn't started to talk by 12 or 18 or 20 months (depending upon how anxious the parent is for the child to develop); and the problems of stuttering and articulation present themselves all through childhood. Most frequently, speech disorders become a major concern to parents about the time when children enter school because that is the point at which the parent becomes more aware of the fact that the child has a handicap that is going to make a social difference.

While studies have shown that, if you take speech disorders generally, most of the disorders occurring in early childhood do tend to drop out as the child grows older and that by 6 or 7 only a relatively small proportion of them persist. As a consequence of the fact that speech disorders do tend to disappear more or less spontaneously in the early period of childhood there is a general impression that all speech disorders will be outgrown—will take care of themselves. That statement is very often made to parents. While it is true that a majority of them do it is of great importance that a considerable proportion do not. It is especially important for the pediatrician to recognize early those cases that may have more serious consequences than the ordinary speech deviations that we find in young children.

The principle reason for the importance of early recognition and early management of these disorders is the fact that speech disorders tend to grow worse with age where they do not spontaneously disappear. The more we talk the more we may be practicing incorrect habits of speech production which will become increasingly hard to change. Then, too, speech is our most important medium of communication. Almost everything the child wants to express and almost every control that he wants to exert over his environment is dependent on speech. If his speech is deviant, he becomes aware of it, others become aware of it, and it then begins at a very early age to have important consequences for him in his personality development. These personality effects of speech disorders tend to become greater and aggravate the disorder itself. If there are steps that can be taken to prevent this, it seems to us important that they be taken as soon as possible.

The pediatrician should be able to recognize when a disorder of speech exists and should be able to identify it. He should know something about the principal causes of the major types of disorder of speech and should know, in general at least, what diagnostic or therapeutic measures may be required by that particular disorder. The purpose of the present discussion is to present as clearly and concisely as possible some systematic information about those speech disorders which are of importance to pediatricians. But before we can proceed to recognize and identify disorders of speech some information concerning the general aspects of speech is necessary because our classification of the major syndromes of speech pathology is dependent on some knowledge of what the basic aspects of speech are.

Dr. Bloomer will take up that phase of it.

Chairman Bloomer: Dr. Strother's comment about the common expectation that all speech disorders will improve spontaneously reminds me of an incident which occurred in our clinic a few weeks ago. The father and mother of a 5½ year old boy who stutters came in because they were very much alarmed about the stuttering. There were certain other factors in his behavior which might have been a little bit alarming too, but the parents had not become aware of these things. It was the stuttering which caught their attention. The mother said the stuttering had gradually increased almost ever since the child started to talk. As a consequence of their concern, and upon the advice of the maternal grandfather, who also stuttered, the parents had taken the boy to their physician in a nearby city and discussed the matter with him. The physician had looked thoughtful for a moment and then had said, "Well, I'd just l-l-let it g-g-go; he'll p-p-pro-obably outgrow it." The mother's imitation of the man was very realistic.

In our consideration of the various types of speech disorders we should bear in mind that speech has both phonetic and linguistic aspects, or stated in another way, it has acoustic and semantic values. Disturbances can occur in any of these phases of speech. We can label disturbances of speech symptomatically according to whether articulation, voice, rhythm or language are affected. Ordinarily,

however, speech pathologists classify disorders of speech under more specific categories of which we shall list 7 for discussion of speech anomalies in children. These categories are: articulation disorders, stuttering, disorders of speech arising from hearing loss, delayed speech, voice disorders, cleft palate speech and cerebral palsy. Aphasia, a category sometimes included in such a list, will be treated briefly during the discussion of delayed speech.

I shall turn now to a discussion of the first of the categories—articulatory disorders. An articulatory disorder refers to the symptoms of sound substitutions, omissions or distortions of vowels or consonants.

Most people ordinarily think of there being 5 vowels. In American speech there are 14 or 15 vowels and diphthongs which are commonly used. We use with these vowels 25 consonants. It is the abnormal production of any of the consonants or vowels that we refer to as an articulatory disorder.

What are the etiologic factors responsible for abnormal articulatory patterns? This is a rather difficult question to answer because there are so many factors which can contribute to this type of speech disturbance. In many instances we have to assume that it is because of some interference with the child's learning; that is, he apparently does not perceive the sounds properly and has not learned to produce the correct articulatory movements. In other instances we have to look for additional factors of a physical or functional type which I shall discuss with you briefly.

Malocclusion of the teeth may affect speech particularly if there is an overjet of the maxilla, an underjet of the mandible, an open bite, or malpositioning of the teeth in such a way that the teeth interfere with tongue contacts at the alveolar ridge. There is not, of course, a one-to-one relationship between malocclusion of the teeth and an articulatory disorder. Many children are able to make compensatory movements of the tongue and lips so that even with a bad malocclusion they can talk plainly. Clinical studies have shown, however, that malocclusion is more prevalent among persons with articulatory disorders than among the normal speaking population.

We must also look for neuropathologies affecting muscular coordination. In these neuropathologies we encounter not only the effects of gross paralysis but also the relatively minor disturbances in which the functions of muscular control are impaired but are not severely affected. Usually in our examination of these children we ask them to perform certain tongue movements. If they can perform these movements fairly accurately and fairly rapidly we feel rather certain that there is no serious deficiency in muscular control contributing to the articulatory disorder. Tests of diadochokinetic movements of the tongue and lips should be employed routinely as a part of the examination.

The function of the glands of internal secretion must also be considered as an etiologic factor since any serious retardation in physical or functional growth may cause a delay in the acquisition of specific articulatory controls. Nutritional deficiencies may likewise contribute.

Hearing loss is another important factor to be evaluated. Even if the loss should occur and continue for a relatively short time it may be etiologically significant if it occurs at a critical period in the child's development of speech. The ages from 2 to 4 years are particularly important and it is quite possible that a child may pick up habits of speech during this time which he will not correct spontaneously even if his hearing returns to normal.

I am not going to touch on the factor of mental retardation at this point except to state that there is a much higher incidence of articulatory disturbance among the severely mentally retarded than among children of the normal population. This statement does not, of course, imply that the existence of an articulatory disorder is any way suggestive of mental retardation.

Deficiency of the palatopharyngeal muscles may be a contributing factor. The palate may or may not be cleft, it may be only a shortened palate or there may be some paralysis of the palate. In any such case it would be difficult for the child to build up oral pressure and the consonants will be consequently weak in intensity or perhaps distorted. The voice quality will, of course, be affected.

Defects in tongue structure sometimes occur but this is not frequently observed. I think that we should bear in mind that for clear articulation one need not be able to move the tongue extensively One needs only to be able to touch the teeth, the alveolar ridge, or the palate to the extent that firm lingual contact is established. I recall seeing a child a number of years ago whose mouth had been severely burned by lye and who was unable to protrude the tip of his tongue at all. He could, however, make enough contact with the upper teeth so that there was nothing acoustically wrong with his speech.

Tongue tie is often thought to be a significant factor and I suppose that many a child has had his tongue clipped as a baby. We have seen few children in whom clipping of the tongue has produced beneficial results.

Question: Have you ever seen any?

Chairman Bloomer: One. I have seen others brought in because it was suspected that they had tongue tie but in only that one case did I feel that clipping was essential.

Question: Can you tell that at birth?

Chairman Bloomer: I can't answer the question categorically. We had a child brought in at 4 months whose frenulum was somewhat shortened. We did not advise clipping the tongue at that time because there was considerable mobility of the tongue tip and we thought that in time it would adjust itself adequately.

The question of a relationship between enlarged tonsils and adenoids and defective speech is often brought up. In many children who have had the operation, improvement in speech has followed. We have seen significant numbers of children, however, for whom no improvement in articulation could be observed following T and A. My own feeling about it is that the removal of the tonsils may have therapeutic value for speech if the hearing is being affected through adenoid growth or if the adenoid tissues are sufficiently enlarged that the nasal passages are occluded and mouth breathing may become habitual. It is possible also that chronically hypertrophied tonsils may contribute to habitual lingual protrusion of the tongue.

In some instances adenoid tissue may even serve a useful purpose by assisting palatopharyngeal closure. It should be retained particularly if there is any difficulty in developing full mobility of the palate. I intend to mention this later in my discussion of children with cleft palate. In the latter cases we usually advise that the adenoids not be removed unless absolutely necessary.

One of the major factors in the etiology of articulatory disorders is emotional immaturity. Recognition of a relationship between speech immaturity and other evidences of immaturity has led to the use of the term "baby talk" in describing the speech of these children, and in this sense it seems to be an apt term. In other words, such children are likely to be immature in other aspects of development as well as in their speech. In such instances we need to assess the environment for its influence on personality and speech development. We need to know whether the child has had adequate patterns set for him. It may be pertinent to inquire as to whether there is a family history of speech defects for it is not infrequently found that one of the parents has had or may still have an abnormal speech pattern.

Dr. Alfred S. Schwartz, St. Louis: Since you mentioned baby talk, lisping, I would presume, would come in there. Would you say that it is indicative of emotional immaturity?

Chairman Bloomer: In some instances, yes.

Dr. Strother: May I add here the fact that in the normal development of speech we don't expect perfect articulation until 7 or 8 or even 9 years of age. Difficulties are quite common particularly with the W, R, and L in the ages from 4 to 6 or 7. A large proportion of these improve spontaneously. It is only if they constitute an obstacle to intelligibility or if they are so conspicuous that they embarrass the child or cause him to be ridiculed that we consider the problem to be a serious one.

Question: Would you let a child start school if he lisps?

Dr. Strother: Yes, I would. I should have added "S" to the sounds that are characteristically slowest to be perfected.

Chairman Bloomer: I shouldn't want to keep a child from school unless his speech were so unintelligible that he would be subjected to ridicule and might develop feelings of inferiority because he couldn't meet the competition of other children.

Dr. Harold J. Freedman, Boston: Under those circumstances would you allow a child like this to get speech training in school?

Chairman Bloomer: We not only allow it but encourage it. In most of the large city schools and in hundreds of smaller communities there are active speech correction programs. I think in most instances the effects of the training enable the child to improve rapidly and to take his place among the normal speaking children. If the matter is handled rightly the child will not have any feeling of adverse discrimination. Most public school speech correction programs start with the first grade.

Dr. Irving Weinstock, Brooklyn: What is the earliest age in which you would attempt to correct a speech defect in the child either by itself or by sending the child to a speech clinic?

Chairman Bloomer: If you are referring to articulatory problems or to general problems there would be a difference.

Dr. Weinstock: I am referring to articulatory problems; the child who is able to make sounds but whose speech is not correct.

Chairman Bloomer: Our advice to parents has varied depending on how difficult it is for the

child to be understood and also some consideration of other personal and environmental factors. If the child has so much difficulty in being understood at 4 years of age that he cannot get along with his playmates (and that sometimes happens) then we would advise some kind of guidance for the child but we do not necessarily place him in a direct therapy program. That is not usually done before 5 years of age. Other clinics vary in their practices, but I believe their decision usually depends on how seriously disturbed the child is and how many other negative factors are present.

Question: Can any harm be done by inadequately trained speech correctionists?

Chairman Bloomer: Yes, certainly a good deal of harm can be done. In this connection you may be interested to know that the American Speech and Hearing Association maintains a classification of its membership according to the levels of clinical competency.

Question: At what age should children be able to perform repetitive speech movements rapidly?

Chairman Bloomer: The ability to control or achieve speech in repetitive movements increases somewhat with age. The child of 5 or 6 may produce 4 or 5 of these repetitive movements, such as pa-pa-pa-pa. By the time he has reached 14 or 15 he has probably very nearly reached adult standards and may be able to repeat as high as 8, 9 or 10 movements per second. You should bear in mind that the tongue tip is very much faster than the back of the tongue. Thus you can repeat sounds ta-ta-ta more rapidly than you can repeat ka-ka-ka.

Comment: There seems always to be a conflict between two factors: (1) a desire for early professional help in speech training for a child who shows some difficulty and (2) the fear that seeking help for that child will make him feel that there is something different about him, and therefore will aggravate the situation. In each individual case I try to decide which is the most important factor.

Chairman Bloomer: The decision is a very important one.

Comment: I think it is most important that we not put the cart before the horse in a lot of these cases, too. Many of these speech defects will stem from emotional problems in the home and if we go after the speech defect per se and forget what is behind it we are merely trying to smooth out the surface without facing the problem. I think that many parents observe the speech defect and they will go after that and will forget there is some reason for it.

Chairman Bloomer: I am glad you made that comment because I want to mention that often speech patterns are important diagnostically—that is, they are symptoms of an underlying problem. Many times the parent recognizes the speech disorder but does not recognize other areas of maldevelopment. He may come to you as a physician for advice about the speech, thus giving you an opportunity to use the speech disorder as a means of establishing a much better physical condition and a much happier home environment. I agree entirely with you that the entire focus should not be on the speech disorder. The child must not be lost sight of among the symptoms which he exhibits.

Dr. Harold D. Lynch, Evansville, Ind.: Dr. Strother, when you mentioned the incidence of speech disability, have you had any statistical evidence to show reading disability in relation to speech disability?

Dr. Strother: There is a significant correlation. A considerable number of children with speech difficulties also have a reading disability. In those cases where the 2 seem to be related, perhaps a perception disability is present affecting both visual perception and auditory perception.

Chairman Bloomer: The fact that there is a rather high correlation has lead me to feel that phonetic (or phonic) methods of teaching reading are superior in assuring good speech development to any of the flash card technics often used. I think there is a current tendency for teachers of reading to return to methods of phonetic instruction.

Dr. Robert J. Mason, Birmingham: So many of these children are encouraged in baby talk and I presume that you have referred to immaturity of their parents and emotional instability of the parents. What is your suggestion to us as pediatricians specifically to override that baby talk?

Chairman Bloomer: I don't believe that the parents' use of baby talk always indicates an emotional immaturity. I think many times parents do not realize that in using a baby talk they may be contributing to the persistence of it in the child. They think it is cute, they like to have the child remain in that small-child-parent relationship and they don't fully understand the effect it may eventually have on speech development. Dr. Strother, do you have any comment on this?

Dr. Strother: Well, if the parent were ready to listen to me, I would say that while this is cute now, the child is acquiring a stronger and stronger habit of talking in this way and it will be especially hard for him to break the habit later on. The time to develop good speech habits is early.

Chairman Bloomer: I wish to sum up our general procedures in advising parents who have children

with articulatory problems. First of all we want to eliminate or treat any physical disabilities contributing to the disorder. Functional as well as structural abnormalities must be improved or compensated. Secondly, if there is any question in your mind as to the adequacy of the environment or the parent-child relationship you may wish to undertake counselling or to refer the parents for guidance. Thirdly, if speech training is available by a competent therapist consideration should always be given to referral for this purpose.

Advice to the parent about what to do in the home would include a request that the parent not stop the child and make him repeat words or sounds which have been said incorrectly. This usually antagonizes the child and has a negative rather than a positive effect. It is better for the parents merely to repeat after the child the correct pronunciation of the word or phrase so that the child hears it frequently in its correct form. The parents can also help the child by rewarding him for improved speech instead of penalizing him in some way for his unsuccessful attempts.

Dr. Strother: I would like to discuss next the difficult and controversial problem of stuttering. First of all, the incidence of stuttering. For the earlier ages, 3 to 7 or 8, the incidence is usually quoted at close to 3%. In adolescence and adulthood, the incidence runs about 1%. There is a marked sex difference in this disorder. The ratio in young children of boys to girls is about 2 boys to 1 girl or 3 boys to 1 girl. By college age, it is about 10 boys to 1 girl. In other words, the recovery rate among girls is much higher than among boys. I am concerned primarily with what I shall call idiopathic stuttering but before I talk about that I would like to differentiate it from 2 other types of stuttering. First, organic stuttering. You are quite familiar with the fact that with brain injury, particularly a cardiovascular accident in older people, stuttering may develop as a consequence of the brain injury. I think the point should be made that sometimes a slight hesitation or repetition in speech may precede any other neurologic symptom of central nervous system disorder. Organic stuttering cases are rare among children. I can't say that I have ever seen a clear-cut case of organic stuttering in children with the possible exception of the cerebral palsy child with whom it is difficult to differentiate stuttering behavior from the dysrhythmia that is part of the cerebral palsy picture.

The second type of stuttering I want to mention is what is called hysterical stuttering. This kind of stuttering is frequently reported in traumatic neuroses of warfare as a temporary stage of the disturbance. Sometimes it is presented as a primary hysterical symptom. In the case of hysterical stuttering, the circumstances surrounding the onset of the stuttering are always emotionally disturbing circumstances but there has been no previous history of speech difficulty. The speech difficulty occurs under conditions of extreme emotional stress. All the other characteristic signs of hysteria are present.

What I want to talk about principally is what we sometimes call idiopathic stuttering—that is, stuttering that begins early in childhood and follows a course that I want to describe in detail, until it arrives at the chronic stage which is seen in practically all the adult stutterers. In idiopathic stuttering, the first stages occur in early childhood somewhere between the ages of 2 and 5 or 6. It should be made clear that, in the process of acquiring the very complex coordinations that are involved in normal speech, a great many children—some people estimate as high as 90 or 95% of all children—go through a stage where they show some hesitation and repetition. That hesitation and repetition will tend to fluctuate with their physical condition and with their emotional stability. Most of them, all except 1 or 2%, go through this early stage of hesitation into perfectly normal speech without any difficulty. We hesitate to call that stuttering at all. It is difficult, in some cases at least, to differentiate this early stage from a hesitation or repetition that is going to develop into something more serious.

We are more concerned about hesitations and repetitions at the point where the child begins to become aware of a difficulty of speech and begins to develop some degree of apprehension about speaking or the speaking situation. As soon as he becomes aware that his speech is different, that the way he speaks is amusing to other people or that his parents are concerned about it, he begins to transform what is normally an automatic process into something conscious—he begins to attempt to control his speech. You know what happens when you attempt to pay attention to your golf swing—it throws everything off because you are thinking so hard about a particular phase that the rest of your sequence of coordination is disturbed. That is what happens, too, when the child begins to be apprehensive about his speech. Not only that but he also begins to be anxious about speech situations. Thus anxiety creates conditions that are not conducive to good coordination.

After the initial stage of hesitation and repetition without apprehension and without any pressure to get the speech out, the child comes into the second stage where he is aware of difficulty. He is

apprehensive, he begins to try to find some way of getting out what he wants to say—to find some way of getting over hesitation. From this stage on we are inclined to analyze what happens in terms of a learning process under conditions of anxiety. In the course of his random efforts to break through the block, the child will go through a number of associated movements. He may throw his head back or blink his eyes or stick his tongue out or go through other movements. When we see children between the ages of 4 and 7 who are going into this second stage of stuttering we see these movements begin to come in. The child ultimately is going to develop a fixed pattern of stuttering. If you watch an adult stutterer you will see that, although he goes through somewhat varied movements, in general the pattern of stuttering for this man is different than for the other stutterers. The particular movements that come to persist are most probably movements that are accidentally associated with breaking through the stuttering block.

I want to mention the fact here that not only is the child acquiring this characteristic habit of stuttering but he is also acquiring what may be the worst part of his handicap, that is, certain sorts of attitudes toward himself and also certain anticipations of stuttering. If he comes to learn, "when I talk over the telephone or when I talk to a stranger or when I do something else I practically always stutter," then he approaches that situation with some anticipation that he is going to have difficulty and the more preliminary anxiety about it there is the more likely he is to have difficulty.

At the stage then when these associated movements—these patterns of stuttering—become fixed, we say the individual has entered the chronic stage of stuttering. Before this, his stuttering pattern has been more or less varied. Now he has come to have a more or less characteristic pattern of stuttering. The prognosis becomes rapidly worse with age in stuttering. If you get children below 5 or 6 and control their environmental conditions adequately, the very great majority will come through with no subsequent difficulty. If the child is 9 or 10 when brought to you, the chances of being able to eliminate this stuttering have become much poorer and many clinicians maintain that if the child has reached adolescence the chance of eliminating all hesitation is practically nil.

Now let me say something about what we probably know the least about—the etiology. There are a number of theories in the field, all of which have some supporters. A good deal has been made of the biochemistry of stutterers and nonstutterers. The research does not tend to support any clear-cut biochemical differences. One of the most influential and certainly one of the most widely known theories has been a neurologic theory, suggested originally by Orton and developed more extensively by Travis, that stuttering has to do with the cortical lateralization of speech. This theory still has some exponents but in the main the research material does not support the notion that there are significant differences in laterality between stutterers and nonstutterers.

Considerable stress has been placed on stuttering as a psychoneurosis. In the military services, it was officially identified as a symptom of neurosis and the individual could be exempted on the basis of a stuttering symptom. The prevailing opinion at the present time is that the development and retention of stuttering is to be accounted for principally on a psychogenic basis and that reduction of the anxiety involved in speaking is the primary goal in therapy.

In concluding what I have to say about stuttering, I would like to suggest what you ought to do about stuttering children. Let us talk now about a child between 2 and 4 or 2 and 5 who is showing hesitations and repetitions in his speech frequently enough to concern a parent, so the parent brings this up for pediatric advice. Let us assume that the child is showing some effort to force through the stuttering block—that some amount of muscular tension and forcing is accompanying his hesitations and repetitions. Let us assume that he is not particularly apprehensive about speaking situations, that he is not much aware of the fact that there is a difference in his speech and that he has not yet begun to develop any persistent associated movement. I am talking now about a child who may be in the primary stage. I would assume that, in such a case, if the environmental conditions are reasonably good, the child is not going to continue having speech difficulty. Notice I said that if the environmental conditions are good. I would interpret the mother's concern over this hesitation and repetition just as I would interpret her concern over feeding or any other difficulty as an evidence that she may be too apprehensive about the child or that too much pressure is being put on the child. I would begin to look into the background of the child's situation as you would look into it if you were concerned about the mother's attitude toward feeding. In other words, look for signs of poor mental hygiene in the home. Then I would try to remedy these undesirable conditions or attitudes. I would watch the child and if the suggestions are taken, if the home atmosphere is

improved, the strong probability is that the hesitations and repetitions will begin to drop out and within a few months the child will show no evidence of stuttering.

Let us now concern ourselves with the child in the secondary stage, when hesitations and blocking become worse, the child becomes aware of difficulty and anxiety develops. At that point we become quite concerned because, unless the right things are done, more severe and chronic stuttering may easily develop. The usual age range in the secondary stage I would say might be anywhere from 4 to 6 or 7—sometimes earlier, sometimes later.

In the secondary stage, we need to concern ourselves with active treatment. This is the point at which we need to begin to look quite intensively into the family attitudes toward the speech difficulty. We need to concern ourselves with the way in which the stuttering is reacted to by all the people in the child's environment and particularly at school. The family and the classroom teacher play an important part in the treatment. In general, the objectives are to reduce the child's anxiety and embarrassment about his speech and to provide speaking situations which are relatively easy for him and which enable him to develop confidence. (Wendell Johnson's *Open Letter to the Mother of a Stuttering Child,* which is available from the University of Iowa Speech Clinic and his book *Speech Handicapped School Children,* available from Harpers Bros., contains material useful for your own reference and for the guidance of parents and teachers.) If there is a qualified speech therapist in the school or community, the child should be referred at this time.

When the child has developed a fixed pattern of stuttering the problem is difficult. The prognosis is significantly poorer than it was in the secondary stage. The child needs to be in the hands of someone who is experienced in dealing with stuttering. The therapy will involve both speech therapy and, at least, limited psychotherapy. Preferably both phases of therapy would be carried out by the same clinician but if the speech therapist is not qualified to do the requisite psychotherapy his work will need to be closely coordinated with that of a psychotherapist. Similarly, the results obtained by psychotherapists who are not familiar with speech therapy are frequently unsatisfactory.

Dr. Sandar A. Levinsohn, Paterson, N.J.: Would you consider hypnosis as a means of relaxing the child in handling the second stage?

Dr. Strother: There is a long history of different treatments—even keeping the child under quite considerable sedation over a period of time. Almost any method which has suggestive value or relaxing value will temporarily relieve the symptoms—and most of the quack schools of stuttering treatment are based on that notion—but in most cases the stuttering shortly comes back in full force.

Chairman Bloomer: The next topic for discussion concerns speech defects due to hearing loss. I should like to point out that since hearing is our way of monitoring our speech, any deficiency of hearing may affect almost any characteristic of speech, depending, of course, on the degree of loss, its type, its duration and the age at which it occurs. There are 3 principle kinds of speech disorders resulting from hearing loss. The first is that of language retardation, second, articulatory defects, third, defects of voice quality, pitch, loudness and inflection. There are also the associated problems such as educational retardation, and personality disturbances which may be caused by the hearing loss and which will also affect speech.

The recognition and proper diagnosis of hearing loss as an etiologic factor in speech defects is often an extremely difficult thing to achieve. It is sometimes hard, for example, to separate a true hearing loss from a failure to respond to sound because of some deep-seated emotional problems. In many instances children who have some degree of brain damage have difficulty in learning and may exhibit evidences of both hearing loss and the direct effects of the brain damage. In these cases it is hard to decide how much of the problem may be due to hearing loss, how much is related to a central loss, and how much to his emotional reaction to the frustration consequent to his difficulty in communication. Thus the problem of properly diagnosing deafness can be a very time consuming one.

Question: In the totally deaf child, to motivate that child to use his vocal chords, is it necessary to establish a painful situation to start this motivation, or can it be done without it?

Chairman Bloomer: I have never known of a painful stimulation being used in any of the better schools for language and speech instruction. As far as I know, the teachers have motivated the child by rewarding him. In my opinion, painful stimulation is not only unnecessary but is reprehensible.

Question: What about hearing aids for the child who is partially deaf?

Chairman Bloomer: We have had good results and I think that most places where they have been

used find that if the child is willing to use an aid especially in the classroom, it will help a good bit if it has been possible to make a good hearing aid selection. I should say something also about the placement of the child in the classroom. This is something we need always to attend to. If he has any hearing loss he should be placed in part of the room where he can see the teacher's face with enough light reflection that he can read lips and also get the maximum use of his hearing.

The need to detect the hard-of-hearing child is of course extremely important. Many a child has failed in school because no one realized that he had a hearing loss. Sometimes the child does not realize himself, yet cannot hear enough of the discussion to keep up with his class.

Question: What is the youngest age that you can rely on an audiometric test?

Chairman Bloomer: If you are willing to take the time, I think that you can go down to 2½ or 3 years of age, with a fair indication of the response.

Comment: The average test is done by the eye, ear and nose doctor. My experience is that they can't do too much under 5 years.

Chairman Bloomer: If the child has a profound hearing loss and you cannot communicate with him then the results in a young child are unreliable. But you can set up a play situation for the child who has usable hearing; for example, you can use audiometric testing by placing the earphone, then giving the child a card that has a bird or animal on it and say "I am going to make the sound of this animal and as soon as you hear the sound I want you to put your finger over his mouth and that will stop him." If you get the child interested in the game, you can get a useful indication of his hearing response.

Question: When should you send the child to a speech teacher?

Chairman Bloomer: If the child is profoundly deaf and you are well convinced of that, I think the instruction should be started as soon as the child and the parents can accept the separation for him to commence special residential or day school training. That may be as early as 2½ or 3 years of age. The parents are fortunate if they have day schools that they can use. There are state schools and private schools such as the Central Institute for the Deaf in St. Louis where they accept young children and are able to accomplish a good deal. Instruction for home training can be obtained from the Tracy Clinic.

Question: Can you rule out deafness in a child of 18 months who has a rich jargon but doesn't say a word?

Chairman Bloomer: I think you can tentatively rule out deafness in that case. Jargon is not infrequently encountered in normal children of that age.

Dr. Strother: I would like to state 2 points in regard to cerebral palsy—the speech training of the cerebral palsy child is simply a part of a comprehensive, long range rehabilitation program and it seems to me, the responsibility for the coordination of that program and for its long range supervision tends to rest on the shoulders of the pediatrician. It involves a great many things, not only pediatric care but orthopedic care, occupational therapy, physical therapy and speech therapy. One thing in particular I would like to say about speech therapy is that from the beginning the kinds of uses the child is making of his oral muscles and his respiratory musculature are important in preparing him for the use of those musculatures in the process of speech.

A recent article by Dr. Harold Westlake in *The Crippled Child* outlines some of the essential steps involved in the early muscle training in feeding situations and other situations around the home where there are a few things that the parents can do. Opportunities to suck and to chew are quite important in developing coordination. If the child is fed and especially if he is spoon fed, and has no opportunity to chew and to suck, he is losing a chance to get some of the early stages of muscle practice that are involved in speech development.

Speech therapy is simply a phase of physical and occupational therapy that is such a complicated and long range program, varies so much from case to case and is so dependent on the details of muscle analysis of the specific kinds of difficulty the child has in carrying out his activity, that treatment must be worked out on an individual basis.

Chairman Bloomer: Before we leave the subject of cerebral palsy I want to add a word. There is a tendency, I think, for parents to be unnecessarily over-protective of these children. The child should be allowed as much opportunity as can be permitted him to develop his own self-help pattern and I think the wise parent will let him feed himself even if he scatters food all over the kitchen or wherever he is placed. He should acquire a feeling of independence.

Dr. Strother: We will now turn to the subject of delayed speech. The criteria of speech retarda-

tion are arbitrary and authorities differ. My own opinion is that if a child does not show comprehension of the names of a few objects or the meaning of some language by 12 months, his speech is retarded; if he is not producing some words consistently, in relationship to certain sorts of situations by between 24 to 36 months he should be considered retarded. We do find some children who do not use single words and then at 2½ or 3 years begin using quite mature speech. In such children, however, one is reassured by the maturity of language comprehension.

Let me say a few things about the etiology of speech retardation. Differential diagnosis in this field is difficult. I think there are more controversial diagnoses in cases of speech retardation than in almost any other conditions relating to developmental status of the child.

The most frequent cause of speech retardation is, of course, mental deficiency. If we take all speech retarded children, the highest proportion of them will be retarded by reason of mental deficiency. Mental deficiency, however, is coming to be recognized as a much more complex condition that it has frequently been considered to be. Technics of examination are just now beginning to develop to the point that we are aware of the multiplicity of the types of mental retardation and the possibility that what we are dealing with in an apparently retarded child is not lack of potential but a lack of development which may be, at least partially, removed by the right kind of treatment. The fact that mental deficiency is a complex problem makes it important for the pediatrician to take a conservative attitude toward apparent retardation and even toward psychometrically established retardation in a child.

Hearing disability, which Dr. Bloomer has mentioned, is not a cause of speech retardation unless the hearing disability is quite severe. With mild loss, the child is still able to develop some degree of language use and some degree of language comprehension.

Another cause which must be mentioned is inadequate stimulation and motivation. If the child does not need to talk then he may be slow in developing speech. The Dionne quintuplets were slow to talk partly because their schedule was so routine and their wants were anticipated so that the need to use language as a way of controlling the environment was reduced. Emotional maladjustment may also be a cause of speech retardation. Immaturity, negativism and autism may affect speech development, as they affect other forms of social behavior. Except in cases of severe autism or of juvenile schizophrenia, children with speech retardation due to emotional maladjustment usually give evidence of substantially normal comprehension of language even though they may not be using any speech.

Finally, I would like to say a few words about what I call idiopathic language retardation but what many people call aphasia. There is real objection to the use of the term aphasia to describe language disability in children because aphasia implies the loss of language due to brain injury. These children have never had any language to lose and, in most cases, no brain pathology can be demonstrated.

We can identify 2 kinds of idiopathic language retardation. The first type affects both the comprehension and the use of language but is considered primarily a receptive disorder. This is termed, in some of the pediatric literature, "congenital auditory imperception" or "congenital word deafness." This is a condition in which the child, although he may not have any hearing loss, still seems unable to comprehend language. He may be able to respond to sound but to learn the meaning of sounds seems to be exceedingly difficult. Often these children have such a lack of interest in sound they appear to have a much more severe hearing disability than they do.

A second type of idiopathic language retardation is characterized either by a fairly fluent gibberish that resembles the paralalia in adult aphasics or by a slow, ataxic, labored articulation that resembles some cases of motor aphasia. In these cases, comprehension may be relatively unimpaired.

In differential diagnosis, several steps are of considerable importance. Under the physical examination, general developmental status should be studied carefully. Neurologic status should be evaluated with particular attention to mild subclinical signs of motor incoordination. A thorough audiologic examination is required to rule out hearing disability. Ewing's work demonstrates that many cases of high-frequency loss are wrongly classified as cases of idiopathic retardation. On the other hand, the fact must be kept in mind that an apparent loss may show improvement as a consequence of speech therapy.

In taking the social history, attention must be given to the emotional development of the child and to the amount of motivation and speech stimulation given in the home. There is available a simple measure of social maturity which will be found helpful. The data required is obtained by interview with a parent and can easily be incorporated in the routine office interview. It yields a

measure of social maturity which is diagnostically useful. For example, if the child's intelligence is normal but his social maturity score is low, it is most probable that the methods of child training used in the home are inadequate.

Question: Where may this test be obtained?

Dr. Strother: I was referring to the Vineland Social Maturity Scale, which may be obtained from the Vineland Training School, Vineland, N.J.

As far as treatment of these cases is concerned an extensive, long-range program is required. Placement in a residential training center may be necessary. The procedures used are those that have been developed for the severely hard-of-hearing or for the brain-injured child—a progressive program of step-by-step acquisition of understanding and of use of language.

Chairman Bloomer: We have a few moments left to discuss speech defects due to cleft palate. If the palate is nonfunctional and the lips and alveolar arch are malformed the main disturbances of speech will involve both articulation of vowels and consonants, and voice quality. I don't have time to say much about the etiology of speech disorders in the child with cleft palate except to suggest to you that all the speech problems cannot be attributed directly to the anatomic defects. In addition to the consequences of the structural abnormalities a child with a cleft palate may have an articulatory, voice or language problem completely unrelated to the cleft. Since he is a human being he is also subject to the many constitutional, physical and environmental pressures which would affect any other child. Some of his speech difficulty may be due to the hearing loss caused by diseases of the ear to which these children are susceptible. There was formerly a much higher incidence of such loss before the antibiotic drugs were brought into widespread use. We must also remember that a factor which influences personality development and hence speech development is the child's own reaction to his noticeable anatomic defect and his reaction to the rejections expressed by his parents or playmates.

I shall try briefly to indicate a kind of pattern to be followed in the management of these children commencing at birth and continuing to maturity. Through the employment of such a pattern you can do inestimable good by using it to guide parents in their planning.

It is important to start early with these children of course. You must start with the parents as soon as they realize they have a defective child. Very often the rejection which follows is profound. If the parent can be led to see that the defect is not irreparable, that it has occurred through no fault of his own and that much depends on his help, he can be brought to provide the normal loving care that any child should have.

Attention to early feeding practices is essential. There is a tendency to want to give the child food by enlarging the rubber nipple holes too much. The effect is thus to feed the baby so that he does not have to perform any swallowing activity and he may not learn to swallow normally. This is a great mistake. It is important that the baby be held for feeding and he be supported in a partially sitting position. He should also be required to do some real sucking. If he has a complete cleft of the palate it is possible to build a little rubber palate attached to a rubber nipple so that it can cover the cleft in his mouth and enable him to establish true suction.

You can of course help the parents by placing them in touch with a good oral surgeon.

Question: Is there any objection in your mind to the very early repair to the lip alone?

Chairman Bloomer: I see no objection to early repair of the lip, provided as much tissue as possible is preserved. Closure of the lip cleft at 4 to 6 weeks will help in establishing normal sucking practice and will aid in molding the alveolar arch. But there are good reasons for not attempting early repair of the palate itself.

Careful attention should be given to the general health of the child from birth and the parents should be cautioned to take more than average care in protecting him from infection.

During infancy there should be a good deal of speech stimulation. The parents should encourage the child to use speech even if he is difficult to understand. This early parent-child relationship is particularly important because these children often need a strong sense of security to carry them through their hospitalization periods for surgical repair of the palate.

We believe that by 2 or 2½ years of age (if the surgeon is willing to operate conservatively) the child may get a good speech result from palatal operation. There is a growing tendency among some surgeons to delay operation because of the fear that they may be disturbing growth centers of the maxilla. Some surgeons recommend waiting until the child is 4 or 5 years of age. In my own experience I have observed that generally good speech results are achieved when the palatal closure

is accomplished in 2 or 3 stages. The surgeon closes the hard palate first and later the soft palate. This is sometimes followed by a set-back operation. An attempt to do the whole thing in one operation is oftentimes too traumatic for the development of good function.

It will be necessary to warn the parents that they must continue with dental care from baby hood on through adulthood. There is a tendency, even among some dentists who don't want to bother with the care of children's teeth, to say, "Let the baby teeth go; they will be replaced by others so you don't need to worry about them." These children cannot afford to lose any tooth, since premature loss contributes to mouth deformity and to speech defects. The permanent teeth are required even if it is eventually necessary to construct a prosthetic appliance.

Chewing habits should be established through the use of food which requires vigorous chewing. The child should be encouraged to suck liquids through a straw to develop vigorous action of the palate. The adenoids should not be removed unless the adenoidectomy is required to preserve the health or hearing of the child. The existence of a pad of adenoid tissue can help in effecting palatopharyngeal closure during the periods most critical to speech development.

Since our time is almost up I want to suggest sources to which you may write for professional help.

The American Speech and Hearing Association may be addressed through Dr. George Kopp, Executive Secretary. His offices are at the Speech Clinic, Wayne University, Detroit.

The organization responsible for many of the pamphlets which you received today is the National Society for Crippled Children and Adults with offices at 11 S. LaSalle St., Chicago.

A majority of the states now maintain public school services to children who have speech or hearing disorders. I suggest that you write to your state department of public instruction for information regarding vocal speech correction services.

Throughout the midwest and the west and in a few of eastern states, you will find that most of your state universities maintain speech clinics which are committed to research programs, professional training of therapists, and direct service to children and adults who have speech and hearing handicaps. You will find them ready to assist you.

I think you can understand our inability to cover thoroughly in one meeting such a large topic as speech disorders in children. We sincerely hope that the information and the discussion have been useful to you.

Pediatrics

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SPECIAL SECTIONS

THE PEDIATRICIAN AND THE PUBLIC

"A forum where discussion could be free, intelligent and continuous."

PAUL A. HARPER, M.D., *Editor*

Statements appearing in this column do not necessarily reflect the opinion of the editor nor are they to be interpreted as the official opinion of the Academy.

THE first communication is by Dr. Franklin D. Murphy, formerly Dean of the Medical School and now Chancellor of the University of Kansas, Kansas City, Kansas; the second is from Dr. Herbert Miller, Professor of Pediatrics at the University of Kansas.

Medicine in Kansas presents a wide range of practice with attendant problems: on the one hand there are large, sparsely settled rural areas where general practitioners carry the brunt of responsibility and where a shortage of physicians has sometimes developed; at the other extreme there is a large and well developed medical school and teaching center where a high degree of specialization is practiced. A major problem is to encourage young men to enter rural practice and then to bring them into some continuous working relationship with the medical center. The people of Kansas have been making strenuous and successful efforts in this direction by the utilization and development of their own resources. The authors, both of whom have been prominent in this endeavor, were requested to describe what this great midwestern state university is attempting to do in this field of medicine.

DEAR DR. HARPER:

The responsibilities of a modern school of medicine and medical center might well be divided into four.

1. Education. Today this education involves training of not only undergraduate and graduate physicians but also many types of professional and semiprofessional personnel in the field of health.

2. Research. A traditional obligation of the medical school, and one which not only permits the acquisition of important knowledge but which also infuses an important ferment into the educational function.

3. Medical Service. This again is a responsibility related to the unique facilities of a

modern university medical center on which physician and patient alike place reliance for the resolution of difficult and special medical problems.

4. Medical Leadership—or Statesmanship. This fourth function implies that a medical school with its highly trained staff has a particular responsibility in working with all groups concerned with health, be they lay or professional. The medical school should have no proprietary interest and should be under no special pressures except those exerted by the body politic, anxious to have more and better facilities and personnel for preventive and curative medicine.

The University of Kansas Medical School has tried to recognize this fourth responsibility in various ways, but particularly in the distribution of medical care. On the basis of objective analysis we have come to the conclusion that there are several significant factors in the reluctance of medical graduates to practice in smaller rural communities.

(1) The modern graduate of a medical school is trained to practice preventive as well as diagnostic and curative medicine with modern facilities. If he has pride in accomplishment, he is reluctant to enter on his work without the necessary physical facilities and tools to do a first-class job. Very often he is financially embarrassed and in debt as a result of a long and highly expensive period of education. He is usually unwilling to compound this debt in order to provide himself these necessary facilities, particularly when in the larger urban centers where such facilities are readily available, numerous opportunities and openings are present.

(2) The young highly motivated medical graduate does not want to become "medically isolated." He does not look forward to remaining far removed from where things are going on medically. He recognizes the need for continuing educational opportunity, and this is most readily available in the large city.

(3) He has the interests of any actual or potential husband or father. He hopes to see his children well educated and hopes to provide for his family a reasonable living experience.

An additional factor which is a background for the total problem of distribution of adequate medical services is our conviction that the country does not have enough physicians to go around. In other words, no matter what steps are taken adequately to distribute medical services, it is difficult "to fill a gallon jug with a quart of water."

Accordingly we have here in Kansas in the last three years developed a program with the following facets. (1) Expansion of our School of Medicine so as to guarantee increased production without impairing the quality of instruction. (2) Working with the Kansas Farm Bureau, Kansas Medical Society, State Board of Health, and other health agencies, we have tried to bring to the various communities of Kansas their responsibilities to create the kind of climate and the kind of working conditions conducive to the attraction of able young men and women. We have found the consumers of medical care, the citizens of the communities, anxious and able to do things but lacking in direction and purpose, which we have tried to provide. As a result, there have been built in many parts of the rural section of Kansas small community clinics for office facilities, well equipped. These have been financed by the local community in a variety of ways and are rented to the young physician. This type of facility is a necessary supplement for the hospital, which is usually located in a larger community, and represents what might be called the first echelon in medical service.

The young physician pays a fair rental for the physical facilities and begins immediately

to buy the equipment from the community out of his earnings, so that in a relatively short period of time he is the full owner of the equipment and may then decide whether he wishes to continue to rent the physical facility or begin to buy it also. Parenthetically, I should point out that we try to encourage these young men and women to start their practices in groups of two or more, recognizing the inherent difficulties in so-called solo practice, particularly in smaller communities.

(3) We have developed a much expanded program of continuation education, designed mainly for the men in general practice, but also containing much of value for the one who specializes. This is a three-point program involving (a) three-to-four day refresher courses in the major fields of medicine, held at the School of Medicine monthly or oftener throughout the year. (b) Circuit courses involving teams of two physicians who monthly give a day's course in eight strategically selected communities in Kansas. Subject material for these courses is more specific and highly practical in character. (c) In-hospital experience of from several weeks to several months to provide "laying on of hands" training, particularly for the men in general practice.

As a result of such a program, one can guarantee, in part at least, the answer to the very real and honest questions raised by a young man looking forward to practice in a smaller community. At least in a fairly high per capita income state such as Kansas, this program has been relatively successful in providing medical services in communities deserving of them.

This is of course only one approach to one problem in the complicated field of guaranteeing our citizenry benefits of modern medical knowledge.

FRANKLIN D. MURPHY, M.D.

DEAR DR. HARPER:

Pediatricians have a big responsibility in the training of students and house officers who expect to become general practitioners, since 75% of the children of this country are today being cared for by general practitioners. The competency with which this responsibility in being discharged is difficult to evaluate, but considering that the general practitioner devotes a third or more of his professional life to the treatment of children, it can readily be concluded that his formal training in pediatrics has not been overdone. As a medical student he may have spent a month or two on a pediatric service and as a house officer he may have served an equal amount of time on a children's ward. Since there is no good evidence that the general practitioner is disappearing from the scene, the obvious challenge in this situation is to make his educational experience fit the type of practice which will confront him in his professional career.

Three years ago the University of Kansas established a preceptorship in general practice. After the junior year each student is required to spend 5½ weeks with a general practitioner who lives in a town of less than 2500 people. These limitations were established, as we did not want the students exposed to group, special or hospital types of practice, of which they see an abundance in medical school. In no sense is the preceptorship a substitute for the student's basic training in medicine. The preceptorship has been added to the regular curriculum and not substituted for something else. The student goes as an observer and as an assistant and not as a replacement for the preceptor. It is expected that the student will come back to the medical center with some insight into the pressures and problems that are the lot of the general practitioner. These problems and pressures

can not be well taught within the confines of a large medical center, for the same reason that no aspect of medicine can be appreciated so well as when the student is personally confronted by the problem at hand. The preceptorship of 5½ weeks is obligatory, but many students elect to spend 11 weeks rather than 5½. The program has been highly successful from both the point of view of the students and preceptors. There have been very few complaints and objections from either group.

One of the very interesting and unexpected results of the preceptorship has been the demand on the part of the returning students for more training in pediatrics and less in surgery during their junior and senior years. They have recognized the disparity between their education and what actually transpires in general practice. Twelve per cent of their time in the junior and senior year is spent in pediatrics in training for a professional life, a third to a half of which will be devoted to the care of children. The senior class last year felt so strongly about this that it petitioned the administration to double the time now given to pediatrics. It is one thing to recognize the need for more time spent in pediatrics and another thing to close the gap. This is not a problem that is likely to be resolved at the department head level or by a curriculum committee, considering all the demands that are being made for additional teaching time by almost every department. Some high authority or some more influential groups like the Academy of Pediatrics or the Academy of General Practice will almost certainly have to exert pressure to change this obvious defect.

Nearly all medical educators have recognized the need for the prospective general practitioner to spend more time in training following graduation and consequently residencies in general practice have been established in several schools. At the University of Kansas it is possible for a graduate to work as long as he wants preparing for general practice. The fact of the matter is most of them go into practice after an interneship lasting only 12 months. Practically all of these individuals would be more than willing to have another year or two of training were it not for the financial problems confronting them. Some system of supporting these individuals should be found. Their value to the community would be enhanced far more than the cost of the additional year or two of training.

The term general practitioner is largely a misnomer. Many such physicians limit their practice or emphasize some aspect of medicine above others. Some do major surgery; others exclude it. Some emphasize obstetrics and others attempt to avoid it. None are too successful in excluding children from their practice. This being so, it seems desirable that a person going into general practice who knows he wants to include major surgery should emphasize this during his training as a house officer. Likewise, if major surgery is to be excluded from his practice, he should and could spend more time on pediatrics and internal medicine. With this in mind the future general practitioner serving as a house officer at the University of Kansas Medical Center is permitted in his interne and resident years to elect how his time shall be spent. This has meant a substantial increase in the amount of time that is devoted to pediatrics in this period, for he knows this is going to be a large part of his practice. It is usual for the person who takes two years as a house officer to spend a minimum of six months and for the one-year man to take at least three months on the pediatric service.

The increased interest in pediatric training in the postgraduate years seems to have originated from experience gained on the preceptorship. Graduates of other schools who have sought interneships in general practice at the University of Kansas Medical Center

have usually not appreciated the significant role children have in a general practice. Some of these graduates have attended schools having preceptorships, but the latter often included work in clinics and hospitals or with specialists or individuals who are considered general practitioners, but are really surgeons or obstetricians doing some general practice. Locating the preceptorship in a small town tends to avoid the above difficulties.

The preceptors claim to have benefited by their position. There has been no lack of practitioners seeking to serve as preceptors. While the program has been reduced from an obligatory 11 to 5½ weeks lately, there is nothing but the strongest feelings on all sides that it should continue.

HERBERT C. MILLER, M.D.

TRENDS

By JOHN P. HUBBARD, M.D., *Contributing Editor*

Statements appearing in this column do not necessarily reflect the opinion of the editor nor are they to be interpreted as the official opinion of the Academy.

PRESIDENT TRUMAN'S HEALTH PROGRAM FOR 1952-53

THE President's January messages to Congress may be looked upon as a measure of the Administration's goals for the ensuing year. In the eighty-five billion dollar budget submitted to Congress on January 21, provision for medical care and public health activities add up to an estimated two billion one hundred million dollars, not counting the sizable but unpredictable sum to be spent next year on international health assistance under Point 4 program direction. Included within this sum is a Public Health Service budget somewhat over three hundred million dollars. Veterans Administration, is down for slightly more than four billion dollars with about seven hundred million dollars earmarked for medical and hospital services (exclusive of construction projects). In the budget for Civil Defense nearly two million dollars is scheduled for stockpiling of medical supplies and equipment.

A comparatively small figure, but one with important significance for the health of children, is an item of $250,000 for grants in aid to states for the development of a program for the fluoridation of community water supplies.

For anyone interested in observing a 10 year trend in government spending in the field of public health, the following figures are most revealing. Here are the actual budget receipts and expenditures (expressed in millions) for the fiscal years 1944 through 1951 and the estimates for fiscal years 1952 and 1953, fiscal year 1952 being from July 1, 1951 through June 1952.

For promotion of public health:

Fiscal year 1944	$162 million
Fiscal year 1945	186 million
Fiscal year 1946	173 million
Fiscal year 1947	146 million
Fiscal year 1948	139 million
Fiscal year 1949	171 million
Fiscal year 1950	242 million
Fiscal year 1951	304 million
Fiscal year 1952	382 million—estimate
Fiscal year 1953	341 million—estimate

Along with the figures, the Budget Message is noteworthy for the health legislation which is recommended and even more interesting, perhaps, for certain omissions. Three points particularly stand out: (1) recommendation for aid to medical education, (2) recommendation for promotion of local public health units, and (3) in contrast to previous years, no mention of compulsory health insurance. In the words of President Truman:

"The health of the American people is essential for our security and development. Like any other resource, health should be safeguarded and improved. The Federal Gov-

ernment has contributed to this objective in a number of ways, particularly through its extensive research programs and its financial aid to the states. But we still have a long way to go.

"On the basis of available studies indicating the pressing need for such measures, I recommend that legislation be enacted to provide aid for medical education and local public health units.

"Furthermore, in order to help outline a course of action which will aid in meeting the long-term health requirements of the nation, I have established a commission to study various health problems. The commission will consider, among other things, the availability of medical services and the adequacy of present methods of paying for them.

"Public health services are provided primarily by local health agencies with extensive cooperation and assistance from the states and the Federal Government. More than half of the Federal expenditures for promotion of public health are for grants-in-aid to the states and localities by the Public Health Service and the Children's Bureau.

"These grants are for such activities as hospital construction, control of venereal disease and tuberculosis, mental health, maternal and child health, general health services and detection of cancer and heart disease.

"Most of the remainder goes toward technical assistance to the states in the form of demonstrations, educational programs and consultative services for the research programs of the Public Health Service and Children's Bureau.

"The estimate of expenditures for health programs in the fiscal year 1953 is lower than for the current year primarily because of smaller outlays to liquidate contract authorizations, particularly under the Federal-State hospital construction program. This reduction reflects our continuing policy of holding new construction to a minimum."

The omission of recommendation for national compulsory health insurance should be viewed in the light of the establishment of the President's Commission on Health Needs with $250,000 earmarked for Commission expense for a one year study. (For review of appointment of Commission see TRENDS, PEDIATRICS, vol. 9, February 1952.)

Also, we may note that Federal Security Administrator Oscar Ewing has recently reminded us that he is as spirited as ever in defense of compulsory health insurance. In a statement before a meeting of the Manhattan Central Medical Society, a New York City Negro medical association, Mr. Ewing stated that, "The plain truth is that the average Negro has less than a fair chance for health because he is not a lucrative patient." He added: "We are not going to change the mind of the individual physician and persuade him to set aside his financial concerns in order to go out and help the sick who need him most . . . and I do not think it would be right." Then Mr. Ewing denounced the American Medical Association for its opposition to compulsory health insurance, and explained how the plan would be expected to work.

PUBLIC HEALTH, NURSING AND MEDICAL SOCIAL WORK

MYRON E. WEGMAN, M.D., *Contributing Editor*

THE article which follows was presented at a symposium on rheumatic fever held recently at The Medical and Chirurgical Faculty of Maryland. It discusses many of the important social problems which may interfere with recovery and rehabilitation and as such is particularly applicable to pediatric practice.

SOCIAL ASPECTS OF RHEUMATIC FEVER

By MILDRED WHITE SOLOMON*

The child with rheumatic fever presents a problem that involves not only himself, his joints and his heart, but the entire family, the parents and the other children as well. All families normally have problems of various kinds; some manage them and some don't. But having a child come down with a serious long-term illness can mobilize these problems, can become the straw that breaks the camel's back. The child and his illness can become the focus not only of the related but all the unrelated and pent-up feelings in the family.

The mother who was previously overprotective of her child will react to the illness in one way; the mother who previously neglected her child will react in another way. Some mothers feel that they must give up their former life entirely, friends and social activities, and devote their entire time to watching over the child and doing things for him. They are being "good" mothers. Others give up nothing, refuse to accept the fact that the child has rheumatic fever and completely ignore it. These I know sound like pretty extreme points of view, but I have found that it is not too rare to find mothers fitting into these pictures. The child's own reaction to his illness will vary with his age, with his personal adjustment at home and outside before he became ill, and with the stability or instability of his family.

The material needs of a sick child are the first ones to be considered. The physical set-up of the home, the financial situation of the family must be up to at least a certain level to assure adequate care. There must be a bed the child can remain in, there must be enough money for adequate food and heat, and there must be an adult in the home to take care of the patient. These things are important and have to be provided before anything else. But even if these material things are available we cannot be assured that bed rest can be provided. These well worn and much used words mean more than just putting a child to bed. You all, I am sure, have seen both children and adults lying in bed as ordered, but getting very little real rest. To feel secure in the love of a family that functions on at least a fairly even keel is more important than a gatch bed or a room with cross ventilation.

What does it mean to a child who has been on unlimited activity to be put to bed? If he is a young child, under six years old, he is at an age when he is working through his relationships with his father and mother, learning to play actively with children his own age, learning to give and take. When put to bed he almost immediately becomes a baby again, dependent on his mother for everything and if this lasts long enough his social

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development can be put back several years. If the child is over six he has already developed some independence from his parents, he is at school a part of a group. This child usually will be pretty angry about giving all this up and there is likely to be a tug of war between his mother and him. If the patient is an adolescent we can look for more trouble as this is an emotionally trying time even if he is well. How many of our children lose all contact with friends their own age while going through a long term illness? The doctor says that the patient can have some visitors but he must be quiet and rest. The mother may say that when other children come into the house they make a mess and too much noise. So they are not welcomed and soon they stop coming in. After 8 months or 12 months the former patient returns to his group but he has lost touch with the goings on that are so important in a child's growth and social development. Then he must either fight to regain his place in the group or else he gives up and lays the groundwork for becoming a cardiac invalid.

Not only the parents but the child needs to understand something of his illness, and the why of what he is told to do. With all the publicity rheumatic fever has had in the newspapers there are few people, children or adults, who do not know something about the disease. But a good bit of this has been written from a pretty pessimistic point of view, stressing it as a cause of death, and sometimes this can be the basis of great anxiety when the diagnosis is first mentioned. It is important to recognize this fear of death when it exists, to bring it out in the open and talk it through not only with the parents but sometimes with the older children.

The meaning of the specific illness to each individual child and his parents needs to be understood and sometimes this takes a lot of listening to and a lot of comprehending of what is said. Some children and even some parents react as if the illness were a punishment for something they have done or thought they have done.

The rheumatic patient, regardless of how young he is, has to be given the opportunity to take some active part in any plans that are made for him if we expect him to carry them through. The degree of his participation will of course depend on his age and his ability to function. Frequently convalescent care outside the home will be suggested. Just picking up a child and taking him to a convalescent home does not automatically settle all problems, even though it might temporarily relieve family tensions. Being moved to a convalescent home can be either a traumatic experience or a growing experience depending on how it is timed and how it is handled. Sometimes weeks of preparation have to be put in before the ground work is laid. It is better to wait to gain the child's confidence and cooperation rather than rush to put him into a convalescent home without his acceptance of the plan. He takes with him his mind as well as his body, his feelings as well as his heart. You can imagine the impact on a child who is taken from his home shortly after his mother has threatened that if he doesn't stay in bed and be good she will send him away—and then it happens. To him this move is not to help him get well—it is being rejected by a family who does not want him.

This is pretty much a cursory sketch of some of the social and emotional factors that are present in families where there is a child with a long-term illness. To a lesser or a greater degree some of these are present in every one of these families, be they rich or poor. The person on whom the whole family depends and to whom they look for guidance is the doctor, the clinic doctor or the private physician. He has the complete knowledge of the medical picture and understands something of the emotional and social components of the illness. In many cases with the time he takes to talk with and listen to the parents

and the child he is able to smooth out the family difficulties that stand in the way of getting a child well. Sometimes he can even keep these difficulties from arising. But sometimes these problems are more complicated and their cause not apparent. They seem to get progressively worse instead of better. The mother perhaps continues her over-anxiety, the child continues to fuss or loses interest in doing anything. I don't want this to sound as though all mothers were problems and everything is their fault. When there is a chronically ill child in the home the mother has a terrific job to do and needs all the understanding and support and sympathy and help she can get. But at the same time the child is having his problems and needs the same sort of help. The problem is really the fact that the illness has occurred and disrupted a family who might ordinarily have managed without outside help. But there we have it and what can be done about it? The doctor may seek the help of a medical social worker to evaluate the situation and get some insight into the family relationships in order to more adequately plan for the child. The medical social worker, because of her training in the meaning and cause of behavior, her understanding of the illness and what it can mean to people, and her skill in the use of available community resources, can help. Then this becomes a cooperative procedure with both doctor and social worker sharing their knowledge of and interest in the family, not two independent people each working off by themselves. The total medical picture includes the social and emotional factors which are in turn either caused by or accentuated by the illness. No doctor, however, gives over the care of his rheumatic patient to a social worker, a nurse or anyone else. This remains a form of team work with the doctor always at the head of the team. This is physically easier to do in a clinic set-up where the doctor and the social worker work together closely and can talk over plans easily. When private physicians use the services of a social worker, some plan for this sort of cooperation will have to be worked out. The services of any or all of the allied professions: the teacher, the vocational counsellor, the nurse, the social worker and the play teacher are available for the use of any doctor when he feels they can help with the care of a sick child. Their goal is the same as his: to get the patient as well as possible without doing too much damage to his personality on the way, and to help him live with his illness and still have a satisfactory and rewarding life.

SPECIAL ARTICLE

CHICAGO PEDIATRIC SOCIETY

Panel Discussion

POSSIBLE RELATIONSHIP BETWEEN PARALYTIC POLIOMYELITIS AND SUBCUTANEOUS INJECTION OF IMMUNIZING AGENTS AND OTHER MEDICINAL SUBSTANCES

Moderator, Dr. Julius H. Hess: I believe the topic of discussion is one of the most serious problems that the pediatrician has ever had to face. It was brought to our attention largely through a series of articles appearing in British and Australian journals in 1949, 1950 and 1951, in which numbers of instances of paralytic poliomyelitis were reported following inoculation. Their conclusions are: (1) that there is a relationship between the time of the last inoculation and onset of symptoms; (2) that there is a relationship between the site of inoculation and the severity of paralysis and (3) that there is a possibility that the inoculation causes paralysis in what might otherwise have been a nonparalytic case.

This has come as a distinct shock to many of us. The pediatricians in the United States have been seemingly slow and somewhat reluctant to accept the statistics contained in these articles as conclusive. This reaction is easily understood when one considers, for instance, the effect that such conclusive statements may have on immunization programs in this country. You will recall that such a program was started in Chicago in 1920 when Dr. John Dill Robertson, then Commissioner of Health, requested a small group of pediatricians to institute hypodermic injections of toxin-antitoxin as a prophylactic treatment against diphtheria. This was later followed for well known reasons by the substitution of diphtheria toxoid. Next to be introduced was pertussis vaccine. Tetanus toxoid prophylaxis in infancy has largely replaced the earlier use of tetanus antitoxin. I need not repeat the story of the effect of this highly successful program on the prevalence of diphtheria, the reduction of pertussis deaths among infants under one year of age, the lower mortality in tetanus and the practical disappearance of typhoid and some of the other bacterial diseases. In Chicago in 1921 there were 9,313 cases of diphtheria with 676 deaths as against two cases in 1950 with one death. (This patient was a transient aged 37 years.)

Now this new situation faces us and the implications are serious. While we were alerted to it by these reports from England and Australia, the growing awareness of the problem in this country is evidenced, in part, by the following:

1. On May 31, 1951, I received a letter from Dr. Harvey F. Garrison of Jackson, Miss., in which he speaks of the "tremendous amount of excitement and concern" in his section of the country over syndicated articles appearing in the press in which "the use of whooping cough and diphtheria shots and booster shots are being given credit for being one of the causative factors in poliomyelitis."

From the monthly meeting of the Chicago Pediatric Society, Children's Memorial Hospital, Chicago, Oct. 16, 1951.

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2. On June 12, 1951, *The New York Times* carried the announcement of the action of the Department of Health of the City of New York to the effect that immunization against diphtheria and pertussis would be suspended in the 76 child health centers from June 15 to Oct. 1, 1951, this order not to apply to infants under 6 months of age.

3. On June 13, 1951, *The New York Times* and other papers issued an announcement of the action of the New York State Department of Health as follows: "Physicians throughout the state are to take particular care in giving any kind of injections to children."

4. While not scheduled for formal discussion at the meeting of the Section on Pediatrics of the American Medical Association, no subject received more serious debate and discussion in informal meetings of pediatricians during the 1951 meeting in Atlantic City.

5. On June 29, 1951, the President of the Board of Health of Chicago, in a meeting with the Advisory Committee of the Municipal Contagious Diseases Hospital, issued the statement that immunizing shots against pertussis, diptheria and tetanus would be continued during the summer in the city's 34 infant welfare stations unless Chicago was threatened with a polio epidemic. This Advisory Committee further recommended that the epidemic proportions of poliomyelitis and not the season in which polio is most frequent should be the guide in determining whether preventive shots are to be given.

We are now faced with a tremendous problem which has an important bearing on the health of the nation. How are we to approach it? Is the immunization program on which we have worked so diligently and with such success to be restricted to certain seasons? Are we to postpone diphtheria and pertussis inoculations, the preschool smallpox vaccinations and tetanus prophylaxis, and diphtheria and pertussis booster shots? Will it become necessary to restrict the use of antibiotics by injection during the summer season? Will it be necessary to bring seasonal allergy inoculations into the picture? These and other questions will be presented, discussed and perhaps answered tonight by the participants in this panel discussion.

PREVENTIVE TECHNIC IN THE ADMINISTRATION OF IMMUNIZING THERAPY

Dr. Louis W. Sauer, Evanston, Ill.: In a timely editorial in PEDIATRICS Faber concludes: "Poliomyelitis with paralysis in the inoculated limb may be due to accidental introduction into peripheral nerves of virus from the patient's own skin (perhaps the more likely explanation), or from previously contaminated needles or syringes inadequately sterilized, rather than to exacerbation and localization of pre-existent infection." Poliomyelitis virus, like the virus of infectious hepatitis, is more resistant to chemical disinfectants such as alcohol and to heat than are cocci. Viral contamination might occur in various ways:

1. Inadequate sterilization of contaminated syringe or needle

2. Sterile syringe or needle contaminated by (a) injector's fingers, (b) injectee's skin site, (c) injectee's fingers

Boiled syringes and needles remain sterile not only for a relatively brief period, but become more readily contaminated than those sterilized in the autoclave or in the hot oven. If assembled while moist, potential pitfalls might make them unsafe, especially during a poliomyelitis epidemic. Contaminated fingers are a potential source when syringes are assembled, and when needles are attached or exchanged, especially if barrel-tip or the body of a plunger is accidentally touched at the time of aspiration or administration of a

dose. When boiling is used, sterile forceps should be used. Should the sterile contents of a vial become contaminated by introduction of virus as a dose is aspirated, and should the preservative in the medicament not be sufficiently potent to kill virus before further doses are aspirated, infection might be transmitted unwittingly.

Syringes and needles are rendered sterile when autoclaved at 120° C. (15 to 20 lb. pressure) for 20 minutes or more, but it is too time-consuming as a routine procedure. For years, we have restricted autoclaving to periodic sterilization of supplies such as small bags of cotton-tipped applicators, cotton balls, gauze squares and wrapped forceps used in needle exchange.

At Evanston Hospital Whooping Cough Research Laboratory, syringes and needles have been sterilized exclusively in the hot oven since 1925. A temperature of 160°C. (320°F) is maintained for one hour. Small, inexpensive gas-heated ovens equipped with thermometers were used for years; recently small electrically heated sterilizers with thermometer and automatic control have been most satisfactory. The technic is standardized so that the same principle prevails whether a single dose is administered in a home, several doses during an office hour, or many at a mass clinic. All-glass or glass with metal (luer-lok) syringes (1 or 2 cc.) and needles (25 gauge, ½″) are soaked and rinsed in distilled water, and dried by suction with alcohol, then ether. Each dry syringe (with attached needle) is placed into a heavy-walled pyrex tube with gauze-covered cotton in bottom and firm, gauze-covered cotton plug. Extra needles, for use during office hours, are sterilized, three, in smaller pyrex tubes. Needles (20 gauge) for leaving in rubber stopper during mass immunizations are sterilized singly in pyrex tubes. When many doses are administered in close succession as in clinics and orphanages, units of 40 needles (point down on gauze-covered cotton pads) are sterilized in monel metal containers. If the lids are sealed securely with adhesive tape while still warm (before removal from the oven), needles will remain sterile for weeks and can be transported with safety. More than the anticipated number of sterile syringes and needles should be available. Oven-sterilized supplies remain sterile for weeks and are available for use without delay.

In children under 3 years of age, alternate lateral gluteal areas (starting with the left proximal) are the sites of choice for administration of antigens. An individual, sterile, cotton-tipped applicator dipped into 1% iodin in 70% alcohol, is rubbed over the rubber stopper and skin site (about 3 cm. in diameter). Ample time is allowed to elapse for the antiseptic to evaporate before a dose is aspirated and before administration. A ball of sterile cotton or square of sterile gauze simultaneously placed over the site keeps the injector's fingers from touching the site as prompt, gentle massage is applied to prevent seepage. In older children, when alternate upper arms may be used, the needle is pointed downward. A square of sterile gauze simultaneously placed over the site keeps the fingers from touching the skin when three distally directed strokes are applied to prevent seepage.

For mass immunization a team of at least four is most practical: (1) Assembles patients and keeps records; (2) Ushers mother and child into and out of injection room; (3) Trained nurse has charge of syringes, needles and antigen; (4) Physician cleanses skin site and administers each dose. At the beginning of each session, before the sterile syringes and needles are touched, the nurse and physician routinely wash hands with soap and water, and dry on clean paper towels. If sterile forceps are not used for needle exchanges, the nurse applies the skin antiseptic to index finger and thumb. As an added precaution, the hands of the nurse and physician avoid touching the injectee.

SUMMARY

Regional poliomyelitis paralysis within a month after hypodermic or intramuscular injection of various medicaments makes a flawless administration technic imperative. If an administration technic without pitfalls cannot be employed, elective immunizations should be postponed during poliomyelitis epidemics.

EXPERIMENTAL POLIOMYELITIS AS EFFECTED BY VARIOUS IMMUNIZATIONS

Dr. Albert Milzer, Chicago: For the purpose of the present studies we inoculated white mice intracerebrally with 10 LD_{50} units of Lansing strain poliomyelitis virus, and the mice were given pertussis vaccine or diphtheria toxoid immunization on the first, third and fifth day following virus infection. The pertussis vaccine was given intraperitoneally in 0.5 cc. amounts and the mice each received 3.75 billion organisms. The animal showed no reaction. Those animals that received pertussis vaccine plus diphtheria toxoid were given 0.25 cc. intraperitoneally, containing 3.75 billion pertussis organisms, and one-eighth of a human immunizing dose of diphtheria toxoid. The other groups of mice which received diphtheria toxoid alone were given 0.25 cc. containing either one-eighth of the human dose of alum-precipitated diphtheria toxoid, or one-twelfth of the human dose of plain diptheria toxoid. All these toxoids and pertussis vaccines were obtained through the courtesy of Dr. Shaughnessy of the Illinois Health Department and were routine biologic products prepared for human use.

The mice were equally divided into test animals and controls. The controls received saline or broth simultaneously after the same intervals as the test animals. There were at least 10 mice in each group and in most instances 20 mice. The reason for doing many experiments is that the incubation period before onset of paralysis with this strain of virus in mice is extremely variable, as can be seen if one compares the controls from experiment to experiment, although the same concentration of virus was used throughout. Furthermore, these experiments were carried out by two technicians working independently. In the first 16 experiments, done by Technician A, it is obvious that in almost all there is a significant difference between the mice which were vaccinated with pertussis alone or diphtheria-toxoid-pertussis combination, and the controls. These results were analyzed statistically by Dr. Herbert Silverstone of Michael Reese Hospital; he found that they were all significant by the Student-Fisher t test, except experiment #16 in which the incubation period was prolonged in the group receiving alum-precipitated toxoid only. The probability values varied from less than 0.01 to less than 0.001 in the remaining experiments. There was no significant difference between the average days of onset of paralysis between the pertussis vaccine group and those which received the pertussis-diphtheria toxoid combination. In 2 out of 3 experiments the alum-precipitated diphtheria toxoid also reduced the incubation period. The results obtained by Technician B are equally significant statistically.

In 1947 we reported that autolyzed brain lowered resistance to polio and facilitated transmission to rodents. We and others have been unable to repeat our results. However, we noted at that time that our stock mice were carriers of Salmonella typhimurium. The infection in the mice was controlled as far as the signs of infection were concerned by means of sulfadiazine; however, the carrier state persisted, and we postulated that perhaps it was the Salmonella infection rather than the autolyzed brain which was responsible for the enhancing effect. In order to test this hypothesis we prepared S. typhimurium vaccine

which was heat-killed and contained one billion organisms/cc. Mice received 0.5 cc. intraperitoneally, at the same intervals as after the pertussis vaccination. The results were suggestive but too variable to be significant. More recently we found that if we inoculated the Salmonella vaccine intravenously (0.1 cc.) at the same intervals, the results were significant. Again, two technicians worked independently, and the results obtained indicate a significant decrease in incubation before onset of paralysis in all experiments except Experiment #1 carried out by Technician B.

Finally, we tested the effect of penicillin and compared it with Salmonella vaccination. The mice received 30,000 units of procaine penicillin G in peanut oil intraperitioneally at the same intervals as the pertussis vaccination. There was no significant difference between the average days before onset of paralysis in the control group which received saline or broth, and the penicillin group, while the Salmonella group in every experiment showed a significant decrease in average incubation time before onset of paralysis. When this work was nearly completed, Findlay and Howard in England reported similar results in experiments in which mice were inoculated intravenously instead of intraperitoneally. More recently, Dean, Cohen and Dalldorf of the New York State Health Department confirmed our findings. They also carried out studies with the Theiler mouse encephalomyelitis virus. These workers inoculated the left front leg with the various vaccines, giving two doses of 0.1 cc. subcutaneously a week apart at varying intervals in relation to the virus inoculation. They found that the incubation period before onset of paralysis was reduced and the frequency of paralysis in the inoculated limb was seven or more times greater than among the untreated controls. This group also found that the supernatant of centrifuged pertussis vaccine had no effect, while the washed cellular sediment exhibited the enhancing phenomenon. Finally, they found that 600 mice inoculated with any of these antigens alone never developed paralysis.

POSITION OF THE ILLINOIS DEPARTMENT OF PUBLIC HEALTH IN THE PRESENT CONTROVERSY

Dr. Leonard M. Schuman, Springfield: No policy developed by a health department is pulled out of the air, nor is it a figment of any individual's imagination. We, too, try to develop field experiments to establish policies and recommendations. The position of any department of health is not an enviable one when frantic parents or local physicians call and ask whether to immunize during August or September, in the midst of the polio season.

Toward the end of 1950 we began a detailed study. In downstate Illinois, almost every case of poliomyelitis is seen by the health officer; even the extent of paralysis is appraised. We asked for specific immunization history in every case, but the returns were unsatisfactory. In 1951, however, the results were much better as seen on table 1. The data was completed as of October 15, and it should be emphasized that the analysis is preliminary. We were able to process 1,079 cases of poliomyelitis for the entire state. So far 1,436 have been reported for the calendar year to October 15. There were 221 of the 1,079 who had no immunization records; in an additional 130 cases there were immunizations but the data was inadequate; the site of injection was omitted, the date of injection was omitted, or the type of antigen itself was omitted. These are being followed by letters written to parents. Nevertheless, on the balance we were able to obtain adequate data.

There were only 19 cases immunized less than one month prior to onset of poliomyelitis, of which 10 were nonparalytic and nine were paralytic in some form—spinal, bulbar,

bulbospinal, and we included the encephalitic. We did not for the purposes of this preliminary report deal with severity in the sense of how many muscle groups were involved, nor the degree of involvement, but rather whether the case was nonparalytic or paralytic in any form.

In Line B of the chart it will be noted that twice as many cases were paralytic after injections one to two months prior to onset. This appears significant. However, the balance of the data reveals little numerical differences between nonparalytic and paralytic forms. When we attempted correlations between two entities (immunized and nonimmunized) on one hand and two entities (paralysis and no paralysis) on the other, we found

TABLE 1

POLIOMYELITIS AND IMMUNIZATIONS—ILLINOIS 1951—PRELIMINARY ANALYSIS
(Immunizations irrespective of type of antigen)

Immunization History	Non-paralytic	Spinal	Bulbar	Bulbo spinal	En-cephalitic	All Paralytic Forms		X^2
A. Less than 1 mo.	10	8	1	—	—	9		.05 A:G .05 A:F
B. 1— 1.9 mo.	5	8	—	2	—	10		0.6 (A+B):G
C. 2— 2.9 mo.	12	3	4	—	—	7		.01 (A+B+C):G
D. 3— 5.9 mo.	22	13	—	—	—	13		.3 (A+B+C+D):G
E. 6—11.9 mo.	21	16	3	1	1	21		.1 (A+B+C+D+E):G
F. Over 1 yr.	265	173	31	8	3	215		.4 F:G
Immunized (No data given)	79	31	14	5	1	51		
G. Never immunized	61	50	2	4	1	57		
No immunization history recorded	87	103	20	8	3	134		
Totals	562	405	75	28	9	517	1,079	

no significant difference between the nonparalytic and all paralytic cases immunized less than one month prior to onset of the disease as compared to those who were never immunized. The same applied to the cumulative period of two months and there was no significant difference at three months. There was a similar lack of significant difference in severity for the longer cumulative periods of six months and one year, as well as for those immunized longer than one year before onset of poliomyelitis. Another correlation was attempted between those immunized less than one month as compared to those immunized more than one year prior to onset. Here again there was no significant difference.

We can say from these data that for this experience to date for Illinois, in 1951, there is no correlation between severity of poliomyelitis and immunizations, at least for injections given in the three month period prior to onset. It is true that the data with respect to the number of limbs involved and with respect to the severity of paralysis of each of these cases on the basis of muscle groups has not yet been analyzed, but on the basis of our studies comparing nonparalytic with all paralytic patients, we believed that we should have found some clues. None were found. For this reason, plus the fact that for the period less than one month but three instances of paralysis in the injected member occurred,

we fail to find a significant relationship. The Illinois Department of Public Health therefore cannot recommend discontinuance of immunizations at the present time.

The question of immunizations can be further resolved by examining the differences in risk of the several segments of the population. Table 2 reveals interesting facts. Taking the worst year in the history of poliomyelitis, 1949, we find that the attack rate for infants under one year of age was only half that of the age group 1 to 14 years. In other words, the risk of poliomyelitis in the infant is only one-half that of older children (it is somewhat higher than for the entire population, irrespective of age, because the bulk of the population is composed of older people who have already developed immunity to poliomyelitis). Even if there were a relationship between poliomyelitis and immunizations, the latter procedure could be applied with greater relative impunity because of the much reduced

TABLE 2

POLIOMYELITIS, ILLINOIS, 1949

	Age Groups (Downstate)			Entire State
	Under 1 yr.	1–14 yr.	All ages	All ages
Cases	74	1,641	2,376	2,910
Population	110,000	1,326,000	5,091,000	8,600,000
Age specific attack rates (Cases per 100,000 pop.)	67	123	47	34
Deaths	4	99	208	231
Case-fatality rate (% deaths to cases)	5.4	6.0	8.7	7.9

chance of attack by the disease in the age group under one year. In fact, this is the recommendation of several other areas in which studies have been conducted. Immunization does not predispose to poliomyelitis. It is merely the question as to the severity of the disease when immunization is performed. I would not go beyond the statements I have already made, and for this reason the position of the Department of Public Health remains the same as that expressed by Dr. Bundesen, or on behalf of Dr. Bundesen by Dr. Hess. We cannot realize the need for postponing immunizations (at least against diphtheria, smallpox and pertussis) in the state of Illinois at the present time, unless we are faced with a major epidemic of the disease, and where the popular pressure is such that it may lead to embarrassment of the Health Department or the practicing physician.

I should like to point out in conclusion that the Los Angeles City Health Department had a similar experience. As a result of their study they too indicate that there is no hazard so far as the very young are concerned.

POLIOMYELITIS OCCURRING AFTER ANTIGEN INJECTIONS

Dr. Gaylord W. Anderson, Minneapolis: Recent English and Australian poliomyelitis studies have indicated that in those children who develop poliomyelitis within a month after antigen injection there is a tendency for the paralysis to be more severe and to involve the extremity into which injections had been given. Some of the investigators found a special relationship to pertussis vaccine. Faber has suggested that virus present in the skin may be carried into the body with the needle.

The present study was based on analysis of the records of children under 8 years of age who developed poliomyelitis in the 1946 outbreak in Minnesota. Histories taken at that time were checked with hospital records and those of physicians and clinics that had given immunizing injections during the six months prior to onset.

Of 85 such cases, 33 (39%) had received their injection during the month preceding onset. Of these first-month cases, 61% showed arm involvement as contrasted with only 21% of those who had received their last injection from 1 to 6 months before onset, 19% who had been immunized more than 6 months earlier and 21% who had never been immunized. Furthermore, 58% of the first-month group showed involvement of the extremity into which the last injection had been given whereas only 15% of the 1 to 6 month group showed such correlation. These first-month cases likewise showed a much higher proportion of bulbar and severe spinal cases and in all instances of multiple-limb paralyes, the injected arm or leg was the most seriously involved. These findings thus bear out the earlier published reports. On the other hand no correlation could be demonstrated between pertussis vaccine and paralysis as many of the group had not received pertussis injections.

All the evidence of this study suggested that the association with recently antecedent antigen injection does not persist for more than a month. In fact there was a special concentration of these cases during the second week after injection with only a normal scattering of cases in the latter part of the first month. When the immunization histories of all the 2709 patients of all ages were examined, there was no evidence that those who had been immunized at some time in their lives had a more severe or a different type of involvement than did those who had never been immunized. While the studies here reported suggest the desirability of postponing immunization during a severe outbreak, there was no evidence to suggest that immunized persons will respond badly to the virus if infected in later years.

A comparable study was made of the effect of injections other than antigen. This latter study was based on all the poliomyelitis cases on which a history had been obtained (2709 with a usual age distribution). The number of these who had received other injections such as tetanus antitoxin, hay fever allergen, insulin, penicillin, etc., was too small to yield conclusive results. While inconclusive, there was nothing in the data to suggest a relationship comparable to that reported above with respect to children who developed poliomyelitis within 30 days after antigen injections. These findings therefore fail to bear out the suggestion of Faber that the virus is carried into the body by contamination of the needle as it passes through the skin. They give no support to the idea that during the poliomyelitis season injections that are therapeutically indicated should be withheld.

Dr. Hess: I should like to give you some data which may be pertinent. Of 544 cases in the County of Cook in 1951 there have been 30 deaths. There were 357 children under the age of 12, 59 cases between the age of 13 and 18, and 128 cases 18 years of age and over. The 128 adults represented 23.5% of the total cases during 1951, and 50% of the deaths were in the adult group. These figures are striking, and show a marked change in age groups in recent years.

Dr. Mark H. Lepper: Our figures at the Municipal Contagious Diseases Hospital are based on 583 patients on whom adequate histories are available in the 1950 and 1951 seasons. Since the figures are similar for both, they have been combined. With regard to penicillin, which is the injection most frequently given, it is difficult to give any accurate data because it is difficult to determine whether it was given during the prodromal period of poliomyelitis or before the onset. According to our figures, 2.2% of the nonparalytic

cases had received penicillin, as did 1.8% of the paralytic patients, before the onset of the prodromal period. On the other hand, 24% of the patients received penicillin injections during the early part of their illness. Of the pure bulbar cases, 23% had received penicillin injections before involvement with paralysis of any type. Among the spinal, or bulbospinal paralytic patients with peripheral involvement, 23.6% had received injections and in the nonparalytic group, 24.5% had received injections.

We also classified the paralytic group as to whether paralysis was in the area of injection only, another area only, or in the area of injection plus another area; whether the are of injection was equally involved, more severely involved or less severely involved. Actually, the differences are insignificant. It seems clear that injections of penicillin after onset of the disease does not influence either the development or the site of paralysis. We do not, of course, recommend giving penicillin during the early part of the polio course; however, we cannot say from these figures that it does any harm and, from a theoretic viewpoint, this is interesting because it does help evaluate the role of traumatic injections on the incidence of paralysis.

A more important problem is the injection of immunizing agents. All cases on which we had records, except one, indicating immunization within two months of admission, had had DPT. It is interesting, too, that in all our histories there is little evidence that injections other than DPT are being given in the community. One paralytic patient had received smallpox vaccination; however, the paralysis was in the arm opposite the one which had been vaccinated. Twelve patients received DPT within two months preceding admission to the hospital. One of these was in the pure bulbar group; eight, or 2.3% of the cases with peripheral paralysis had received DPT; three, or 1.7% of the nonparalytic group had received DPT. Again, there is a little trend toward having paralytic cases in the DPT group. Similarly, when we compare the areas involved, five patients had only the area which had been injected involved with paralysis. This is 63% of those who developed paralysis following DPT. Two, or 25%, had paralysis of totally different areas and one had paralysis in the same area plus other areas of approximate severity.

Thus our figures to date indicate that perhaps there is a slight tendency to localize to the area of injection, but that the over-all risk of contracting polio is not great. Of the five paralytic cases, four were in the age group below one year, one was in an older child who received a DPT booster. Of the four infants, three had transitory paralysis, that is, by the time the patient was ready for discharge the paralysis had cleared up sufficiently to be insignificant. In only one case did we have to transfer the infant to another hospital for further treatment.

For these reasons, we feel that this is not a serious problem. It is one that merits consideration, particularly in time of epidemics, because you can multiply these figures any time the incidence of polio increases to the point where there is a significant number of patients.

Dr. Archibald Hoyne: During recent years the complexities of poliomyelitis have been accumulating at an accelerated pace. Now we must consider the relationship of injected antigens to poliomyelitis. On the basis of the evidence available it does not seem justifiable to reject totally the possibility of some association. Certainly the investigation conducted by Dr. Anderson and the reports of others have seemed extremely interesting. The element of trauma at times has been considered by parents as a contributing factor in bringing on an attack of poliomyelitis; however, such a theory has usually been discounted by physicians. If pertussis vaccine is eliminated as the principal offender, it would seem that trauma to

the muscles and not the particular contents of the syringe is the inciting cause of trouble. Nevertheless, if such is the case one would expect a number of reports following intramuscular injection of penicillin during the poliomyelitis season. I am aware that our main topic relates to subcutaneous injections. But with subcutaneous injections we might be able to prove that some injury to underlying muscles did occur. Under any circumstances it would be interesting to determine whether the reported influence of immunizations on poliomyelitis would be eliminated by injecting antigens intracutaneously during the poliomyelitis season. Immunization by the oral route is of little or no value.

There have been no patients with poliomyelitis at Cook County Hospital this year who have received any immunizing injections within 30 days of onset of illness. Possibly we will learn eventually that the deleterious effect following the injection of antigens during the poliomyelitis season does not occur unless the patient harbors the Coxsackie as well as the poliomyelitis virus. That explanation may be advanced in 1952.

Dr. Ralph Spaeth (with Dr. Martin O. Sacks): During a 10 year period, about 10,000 injections of alum-precipitated diphtheria-tetanus toxoid (pertussis omitted) were administered to about 3,000 foster children under the care of the Chicago Welfare Association, in the age range of 2 to 21 years. Five cases of poliomyelitis occurred. In none of the patients could the times of onset (4 to 6 months after injection) or the sites of involvement be related to the inoculations. All injections were in the arms, usually the left, and the paralysis appeared in the lower extremities in three cases, in the upper extremity in one, while neuromuscular involvement was absent in the fifth (nonparalytic).

In private practice, 760 subjects received about 1,100 immunization procedures during the months of July-September inclusive, in the five year period ending in 1950. One five year old boy, who had received a recall injection of 0.5 cc. triple alum-precipitated antigen (pertussis, diphtheria, tetanus) in the right deltoid region, developed a clinical picture of dromedary poliomyelitis. The syndrome became one of mild bulbar involvement with complete paralysis of the right upper extremity and mild weakness of the left arm and both legs. Recovery to date (13 months later) includes all but a flail upper right extremity and weakness of the left anterior tibial and short flexor of the left thumb.

About 50% of the immunization procedures in our group consisted of alum-precipitated triple antigen. In a group of 400 inoculations (300 of diphtheria-tetanus and 100 of pertussis alone), no difficulties were encountered. It is significant that 253 infants under one year of age received routine inoculations, starting at 5 months of age, without the appearance of clinical poliomyelitis. One case associated with smallpox may be a possible exception. The factor of limited exposure to poliomyelitis virus in private practice among infants is probably pertinent. The desirability of starting the injections during the earlier months (two months or later), when a high incidence of passive immunity is to be expected, might be reconsidered as an added measure of safety.

A noncorrelated case occurred among a group of 49 subjects given smallpox vaccination. The patient had received four doses of alum-precipitated triple antigen during the months of March-June, 1949. At the age of 10 months the patient started to walk alone. At the age of 11 months he developed a primary take in response to smallpox vaccination. Within a month after vaccination he stopped walking, only to resume walking at the age of 13 months, with a definite limp involving the left lower extremity. At present he has weakness and atrophy of the left lower extremity, although he is able to walk with the aid of an appliance. It is pertinent that in June 1949, between the last two injections of triple antigen, he had what appeared to be a mild upper respiratory infection. The possibility of

an unrecognized poliomyelitis must be considered. Moreover, it is of interest that the paralysis appeared at a site remote from the smallpox vaccination.

I would like to propose the establishment of a central registry for reporting statistics from private and public welfare practice, properly selected geographically, seasonally and otherwise, in order to assist in clarifying the problem.

Dr. Harry L. Faulkner: The following three cases are presented from my private practice. The first, a boy aged 7½ months, was in good general health although during the first three months of life there had been some evidence of allergy. In August and September 1950 he was given two injections of 0.5 cc. of DPT alhydrox, the first in the left triceps with a 5/8 inch needle, the second in the right triceps. No local or systemic reactions occurred. Twenty-one days after injection he developed an intestinal upset which apparently improved within 24 hours, but within the next 24 hours the symptoms returned and he was found to have a moderately stiff neck, head drop and weakness of the right arm and shoulder girdle. Following spinal puncture the diagnosis of poliomyelitis was confirmed. He subsequently developed weakness of the left leg which cleared within a few months. The right upper arm is still flail after one year, but there is no other evidences of poliomyelitis.

The next two cases are presented together because of their similarity. A boy aged 6 months, the son of a physician, and a girl, aged 6 months, the daughter of a nurse, lived in adjoining apartments. These children had been under my care since birth and their development had been normal. They were always cared for by one or the other mother, except on one occasion. On October 27, 1949, each was given the first inoculation by the boy's father. The girl was given 0.5 cc. DPT alhydrox from a 10 cc. vial which had been and was subsequently used for inoculation of other children in my practice. The boy was given 0.5 cc. diphtheria-tetanus toxoid from an individual vial. Both injections were given in the right triceps with a 5/8 inch needle. There were no local or systemic reactions. Fourteen days later both children became ill at approximately the same hour, with an intestinal upset and fever which lasted 36 hours. On November 12 both children were found to have a stiff neck, head drop and weakness of the right upper arm. Following spinal punctures the diagnosis of poliomyelitis was confirmed. The girl developed no other paralysis while the boy developed some in both lower extremities which later cleared up. Two years later, both children still have a completely flail upper arm and shoulder girdle.

Special precautions were taken by this physician father in preparing the injections. The needles and syringes were surgically sterilized and new needles were used. Preparation of the site of injection was meticulously done with soap and water, alcohol and ether.

It is impossible to say that the injections had any part in the development of paralytic poliomyelitis in these three cases. However, with the evidence collected by the British investigators, one might be inclined to suspect that the trauma caused to a muscle by injection of a foreign substance makes that muscle more susceptible to paralysis in case the child develops poliomyelitis. There is no reason to suspect that an injection of any kind will make a person more susceptible to poliomyelitis. However a nonparalytic or abortive case might be made a paralytic case as a result of a recent injection of a foreign substance.

Dr. Martin H. Seifert, Evanston, Ill.: We have had on the contagious disease service at Evanston Hospital this year approximately 150 cases of poliomyelitis. I was able to analyze 135 of these, on 15 of which we were unable to get records of whether injections of any kind had been given. There were eight patients who had had injections within recent months; six had received DPT, none less than six weeks before. One of the eight

had received antigen for hay fever, and one was a diabetic patient who received insulin daily.

Two of the cases were bulbar, three were nonparalytic, one had paralysis in the right arm and one in both legs. The only severe case was the one who had hay fever shots, which supposedly are innocuous.

It is interesting to note that 45 of the approximately 150 cases were adults, and of our deaths 10 were adults.

I believe we should pay attention to one other point in relation to any conclusions about this matter of localization of paralysis; that is, we must extend our observations and experiences over a period of years. Those of us who have seen polio over a period of years are all too aware of the tendency for polio to form patterns year after year. This year would be a good year, in an area where a large number of injections are done in the arms, to conclude that the arm was affected because of the injection of an antigen. We have had an unusual incidence in our group of involvement of one or both upper arms and shoulders. That has been the most definite pattern we have had. However, I do not believe we can draw conclusions from any one year's epidemic.

As to whether needles transmit the disease—it seems to me there should be many cases of polio in the practices of those who are in intimate contact with it a good part of the time. Yet, in spite of the fact that I handle many cases at the hospital, I do not think I average a case every other year in my own practice. It would seem that if there were any great likelihood of transmission of poliomyelitis by needle, I would see more in my private practice. The only one I had this year was a lad of 18 whom I had never seen professionally before.

Dr. Herman N. Bundesen (President, Chicago Board of Health): We have found in Chicago that inoculations against diphtheria and pertussis have prevented countless numbers of deaths, and it is with extreme hesitation that we would consider abandoning these procedures even for a short period. This excellent result in the reduction of deaths from diphtheria (1,228 in 1917, one in 1950) has been brought about only by our intensive program of inoculations with diphtheria toxoid. In 1950, there were 1,165 reported cases of pertussis and two deaths. It is only in the last several years that the program of administering pertussis vaccine to large groups of infants has been intensified, starting when they are 3 months of age.

More than 85% of our infants and children have received diphtheria toxoid, and we feel that to attain complete control of diphtheria it is necessary to maintain this high level. Were we to discontinue inoculations during the poliomyelitis season, or for some 3 or 4 months, the burden placed on the physicians of Chicago and the Health Department nursing personnel in catching up with not only the primary immunizations but also the giving of booster doses would be almost insurmountable. Failure to maintain the program would undoubtedly lead to an increase in the number of cases and deaths from diphtheria. We know this from past experience.

Chicago has not been faced with any abnormal prevalence of poliomyelitis recently. There is of course a seasonal increase in the number of reported cases each year, starting about the first of July. We have come to expect from 300 to 500 reported cases, and with increased diagnostic skill it is to be expected that the number of nonparalytic cases reported will continue to increase. Thus far in 1951, 58% of the cases reported are nonparalytic, while in 1950, for the same period to October 15, only 48% were nonparalytic. In the meantime, we do not feel that there is any reason for general discontinuance of

immunization during summer months. We hesitate to take any measures which may cause the public to associate inoculations against diphtheria and pertussis with any risk of danger. Should there be a marked increase in the prevalence of poliomyelitis in Chicago, however, it would be necessary for us, after consultation with our advisory board, to determine whether continuance of the inoculation program presented a greater hazard than the loss of life which might occur should the program be temporarily discontinued.

Dr. Clifford Grulee: I think what Dr. Bundesen has just said is the crux of the situation. It is not a question of whether, by giving these injections, we do promote a little more polio than occurs normally, but it is a question whether lives are saved by giving injections of diphtheria toxoid and pertussis vaccine and so forth; where there is not a greater risk to the community by not doing this, than by giving injections during a polio period.

Dr. Winston Tucker (Commissioner of Health, Evanston): I agree heartily with Dr. Bundesen and Dr. Grulee.

Dr. John B. Hall (Director, Cook County Board of Public Health): Dr. Bundesen and Dr. Shuman have expressed my views.

Dr. E. A. Piszczek: I would like to stress what Dr. Seifert said: we cannot judge polio by any one year's records or experiences.

In 1943 we had our worst year in Cook County; 1,262 polio cases and 108 deaths. At the same time we were fighting a diphtheria epidemic in Chicago. There seemed to be no correlation whatsoever at that time, but this presents a factor which makes comparisons difficult.

The significant factor in this study of immunization in relation to polio is that we may be increasing the number of contacts with children who are sick. In England, I understand, doctors do not make as many home calls, but patients are brought to the doctor's office. That might be a factor for American medicine to study, for in the last three years Dr. Hall and I have seen three cases of polio that originated by contact with another case in the doctor's office. We know this is unusual but, nevertheless, it is a factor to be reckoned with. I think we should stress the fact that if polio does occur the first month after inoculation it might be due to this increased exposure. I think we should continue to immunize, but we should observe the problem for 4 or 5 years before we draw too many conclusions.

To lessen the trauma, it might be possible to reduce the number of multiple injections for pertussis, diphtheria and tetanus and give single injections of the individual immunizing agents. This year many parents have been very cautious about immunizing their children and, as a result, I think we have seen an increase in pertussis.

Dr. Spaeth: I would like to ask Dr. Milzer whether ordinary sterilization with water could be made equal to the autoclave, or is water sterilization obsolete?

Dr. Milzer: As far as the polio virus is concerned, Dr. Shaughnessy and his associates at the University of Chicago showed that heating at 60° C. for 30 minutes will inactivate the various strains of virus; this finding has been confirmed recently by Melnick at Yale. Therefore, boiling for 5 to 10 minutes should inactivate the polio virus. But this procedure will not sterilize a syringe, because spores are not killed. The way to kill spores is to sterilize in the autoclave at 121° C. for at least 20 minutes, or hot air sterilization may be used as Dr. Sauer emphasized.

As I said, I have been working with a mouse strain of poliomyelitis, and I think from the point of view of the experimental work, these antigens seem to be a definite factor

in lowering resistance. If they are given a week or two prior to virus inoculation, they have much less effect on the course of the disease. I think one speaker mentioned that Dr. Faber postulated that the infection comes from virus on the skin, and inoculation through the skin causes the virus to penetrate the nerve endings and migrate to the nervous system. Another theory is that perhaps the syringe or needles are contaminated with polio virus. A third theory is that the virus is already present in the host and the injection produces a locus minoris resistantiae.

It is true that we have given tremendous doses of vaccine to these animals, but I would like to correct the fallacious idea held by many physicians with regard to immunizing animals. One cannot immunize animals with the same dose of antigen on a weight basis that is used in immunizing human beings. This fact is reflected in the National Institute of Health tests for potency of typhoid vaccine, rabies vaccine, and so on. In these tests much larger amounts of vaccine are given on a weight basis than is recommended for human beings.

Dr. Schuman: Dr. Seifert's remarks struck home. It may not be known to you that at the present time, 1951, the Chicago area seems to be experiencing a somewhat more severe form of polio than elsewhere in Illinois. This does not mean you are having more or a greater incidence of poliomyelitis than the state as a whole, but rather that in comparison it is relatively more severe. Yet in 1949 the reverse was true; downstate Illinois experienced more severe types of poliomyelitis and more cases than did Chicago. The comment that Dr. Seifert made about peculiar configurations should therefore be emphasized.

I should like to point out again that there is also corroboration of the points Dr. Anderson made in our data for Illinois; namely, that for those immunized over one year as against those who were never immunized, the correlation is completely insignificant. Furthermore, in the eight spinal cases we have record of, only three had paralysis in the site of injection, two in the arm and one in the leg.

Someone suggested a registry of immunizations. I agree that if this could be made to work effectively, we could then have an accurate source of data.

Dr. Anderson: Dr. Piszczek raised the question of the possibility of contact in the doctor's office. That question has been raised by some of my friends; I did not wish to raise it because I am not in practice and they are. I would doubt very much if that was a factor in the series we had. Though that might explain why we had a few more cases in the first-month group, it would not explain why the distribution of paralysis was different. I would not expect the virus spread in a doctor's waiting room to differ from that under other conditions, and I do not think there is reason to think the portal of entry is any different when spread in one place than in another.

The question of a registry has been raised. I would agree that it would be highly desirable, but am rather dismayed at the thought, knowing how difficult it is sometimes to get reports from various groups. I am afraid we would not get too far. It would seem that with respect to poliomyelitis and immunizations we are in practically the same situation as with poliomyelitis and tonsillectomy. Undoubtedly it is a rare association. Thousands of children are immunized during a polio outbreak and only a small fraction will come down with polio. The question is, not how many come down, but rather, is this one extra risk we are adding to the child. The situation is comparable to that of the physician dealing with a case of dog bite. He must decide whether to give rabies vaccine. On the one hand, if he does not give vaccine the child may develop rabies; if he gives

vaccine there is a risk of vaccine paralysis. He selects that which seems to him the lesser of the two risks. We are in the same situation; if we withhold immunization there is the possibility that the child may, in the next few months, develop diphtheria or pertussis and die from it. If we immunize in the face of an outbreak there is the risk that this may be one extra factor adding to the likelihood of a paralytic manifestation. Obviously we must make our decision on the basis of what seems to us to be the lesser risk. We cannot possibly say there is no risk in either case.

As Dr. Bundesen pointed out, the recommendations of the Committee of the American Public Health Association was made in terms of an increased and abnormal prevalence. The recommendations were so worded because all the data that were available, both published and unpublished, were gathered during a period of abnormally high prevalence. The Committee frankly stated, "We don't know what the risk is in a period of normal prevalence or subnormal prevalence." The Committee felt that it could say that during a period of abnormal prevalence the lesser of the two risks was that of postponing immunization for 2 or 3 months. It did not feel that it was entitled to an opinion, nor do I think we are as yet entitled to an opinion, as to what to do in the absence of an outbreak. I agree with Dr. Bundesen that in the absence of evidence that there is an increased risk during periods of reduced or normal prevalence, we are not justified in going off the deep end as some of our friends did in New York, in calling off all immunizations. It was extremely unfortunate as the newspapers headlined it on the front page, thus frightening people about immunization. We have to live that down and try to keep a proper balance in the entire controversy.

Dr. Hess: We have heard excellent discussions on the many facets of this problem by men well qualified to speak. The following statement from the National Foundation for Infantile Paralysis might be of help in clarifying our thinking:

"The possible relationship between paralytic poliomyelitis and injections for immunizing against whooping cough, diphtheria, tetanus, or injection of other biological and medicinal substances recently has been the subject of intensive study by English, Australian and American workers. The studies do *not* show that injections for the prevention of whooping cough, diphtheria, tetanus or injections of other medicinal substances are the *cause* of poliomyelitis. The great majority of cases of poliomyelitis give no history of recent injections. There is no evidence that poliomyelitis infection is any more frequent among persons who receive such injections than among those who do not. The possibility that an injection may in some way tend to convert an otherwise nonparalytic into a paralytic infection should be considered although it lacks proof. If established, it would mean that an injection of any of the substances mentioned, at a time when poliomyelitis is abnormally prevalent in the community, may entail some small added risk to the person receiving it. There is no reason to believe that the added risk would extend beyond the month immediately following the injection, or that any added risk exists at all if injections are given at a time when poliomyelitis is not prevalent in the community. The relative risks of giving or withholding an injection must be weighed in each individual case. Studies on the relationship of paralytic poliomyelitis to injections of medicinal substances have not been completed nor have the results been properly evaluated as yet. Results reported to date are tentative and should not be considered at this time as final evidence. They should be considered only in the light of a warning against indiscriminate injections during periods of poliomyelitis epidemics."

In closing, I can only say that as pediatricians it is our duty in the future to study all cases of paralytic poliomyelitis with particular reference to: (1) the date of past inoculations; (2) the age of the patient and, (3) the prevalence and severity of the poliomyelitis epidemic. If we do this, it is possible that at some future meeting of the Chicago Pediatric Society, a review of our findings and statistics will give us firmer ground to stand on and more definite and conclusive evidence that we are headed in the right direction.

SPECIAL ARTICLE

AMERICAN BOARD OF PEDIATRICS

STATISTICAL analysis of the January 1951 written examination of the American Board of Pediatrics has been completed. The following comments are offered for general information.

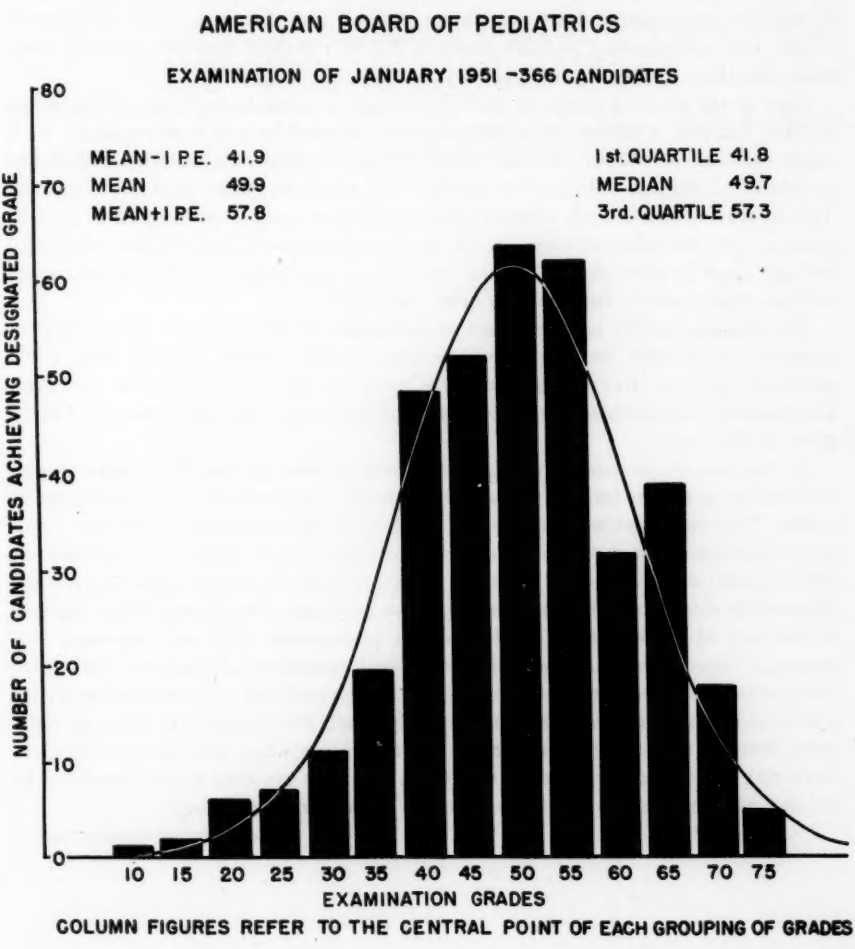
Like the examination of January 1950 (see PEDIATRICS 8:598, 1951), this examination also consisted of 200 false and true statements. It was a completely new examination, that is, none of the statements contained in it had appeared in previous examinations. Tabulation of the responses of all the candidates to each of the 200 items disclosed the fact that some of the statements had been poorly phrased, that some of them dealt with details of disease with which the vast majority of candidates were unfamiliar, that some few were answered correctly by 99% of the candidates. Such statements do not contribute to the accuracy of grading. They are, however, unavoidable before new statements have been tested on the candidates. The committee charged with preparing the examination is aware of this weakness and will continue to assemble statistics and comments toward the objective of reducing the number of poor questions to a minimum.

The examination was taken by 366 candidates. The method of grading was the same as has been used in the past, that is, to the number of correctly answered statements is added half the number of unanswered statements and from the total 100 is subtracted; the remainder is the grade. The distribution of these grades is shown graphically in the histogram (see chart 1). Superimposed on the histogram is a normal frequency curve the

Grade on written examination	Decision after oral examination			
	Passed	Failed	Total	Passed
				per cent
Lowest (1st) quartile	30	30	60	50
Next to lowest (2nd) quartile	67	12	79	85
Next to highest (3rd) quartile	75	2	77	97
Highest (4th) quartile	76	4	80	95
Total	248	48	296	84

ordinates of which were computed from the mean and standard deviation of all the grades. The observed frequencies do not differ significantly from those to be expected in a normal distribution. Normality of distribution is also suggested by the essential identity of the ranges defined on the one hand by the mean plus and minus one probable error and on the other hand by the positions of the first and third quartiles. The range covered by the mean plus and minus one probable error embraces 50% of the grades; this range was 15.9 points as compared with 14.9 points for the 1950 examination. Although the distribution of grades was essentially the same for the two examinations, the 1951 examination was on the average more difficult than the 1950 examination; the mean grades were 49.9 and 55.6, respectively. For the 1951 examination the lowest grade was 11.5 and the highest grade was 75.

The following comments are in order on the foregoing paragraph. Examinations which yield a normal distribution of grades are in general more satisfactory than those giving other distributions in assigning rank order to all of the candidates. The purpose of the examination is not, however, to assign rank order but rather to select those candidates who are relatively weak in their knowledge of pediatrics. The Committee is not at this time



interested in using its written examination to pick out those deserving honors. It is striving to develop a test so good that a passing grade can be demanded before a candidate is permitted to appear for oral examination. Ideally, this test will be relatively insensitive in establishing rank order for the top grade candidates but correspondingly more sensitive in selecting the order of the low grade candidates. It will not yield a normal distribution of grades.

In our previous report a method of statistical analysis was described which permits computation of a "standard error of assessment" or "standard error of measurement" or "S.E.M." of an examination. This S.E.M. is the ultimate measure of the efficiency of the examination in defining the position of the individual candidate against the background of all of the candidates. It is the statistic in terms of which the relative value of all subsequent examinations must be assessed. The analysis discloses that the S.E.M. of the 1951 examination, 4.932, was almost identical with that of the 1950 examination, 5.028. The corresponding probable errors or P.E.M.'s derived from the standard errors were: for 1951, 3.326; for 1950, 3.391.

Since in the previous report an error in printing occurred in explaining the meaning of these statistics, a portion of the explanation is repeated here. If it were possible for a single candidate to take an unlimited number of similar examinations, each based on 200 statements of identical difficulty, the average value of all the grades would be a constant. This constant is conveniently termed the true grade. For a single examination of the type given in 1951 the odds are even, i.e., 50-50, that the assigned grade will not differ from the true grade by more than 3.326 and the odds are two to one that the assigned grade will not differ from the true grade by more than 4.932.

The essential identity between errors of assessment calculated for the 1950 and 1951 examinations probably means that we are close to what can be expected from a 200 statement false and true examination. The errors are still considered to be too large. Consequently, examinations composed solely of false and true statements will not be given in the future.

At the time of preparing this report the final decision of the Board after its oral examination is known for 298 of the 366 candidates who took the 1951 written examination. Two candidates were conditioned in "growth and development" and must come up for re-examination in this phase only of pediatrics. For the other 296 candidates the final decisions of the Board are presented in tabular form. Candidates appearing for oral examination should know that the examiners who interrogate them have not been apprised at the time of grades earned on the written examination. However, impressive discrepancies between the opinions of the several oral examiners and grades on the written examination constitute one of the reasons why some candidates are asked to remain for additional oral interrogation. The Board frankly admits the possibility of errors of judgment after its oral examination but adheres to the conviction that ultimate decisions concerning the fitness of candidates to practice pediatrics are more justly determined by oral interrogation than by any type of written examination yet devised.

THE EXAMINATIONS COMMITTEE

NEWS AND ANNOUNCEMENTS

Dr. Arthur J. Lesser has been appointed director of the Division of Health Services of the Children's Bureau, Federal Security Agency.

Dr. Lesser succeeds Dr. Edwin Daily, who resigned to become Deputy Medical Director of the Health Insurance Plan of Greater New York.

As director of health services, Dr. Lesser will be responsible for the administration of the maternal and child health and crippled children's programs of the Children's Bureau.

ERRATA

Special Article, American Board of Pediatrics, PEDIATRICS, vol. 8, October, p. 600, line 19 should read: "true grade by not more than 3.39 and the odds are 2 to 1 that the assigned grade will differ from the true grade by not more than 5.03. . . ."

Pray, L. G., Congenital dislocation of hip, PEDIATRICS, vol. 9, January, pp. 95, 98 and 99. P. 98, Figs. 3A and 3B should be transposed. P. 99, Figs. 4 and 5 should be transposed. P. 95, para. 3, line 6 should read "is abducted." P. 99, after line 13, the following should be inserted after "or to": ". . . follow a cast after partial correction has been obtained. The open shelving operation may . . ."

Glichlich, Lucille Barash, An historical account of enuresis, PEDIATRICS, vol. 8, December, p. 873. The second paragraph should begin: "Kanner[58] described theories, to which he does not subscribe, wherein enuresis in the male is a form of identification with the father. . . ." The fifth paragraph on the same page should begin: "Kanner[58] also described the theory that female enuresis is an expression of the castration complex. . . ."

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